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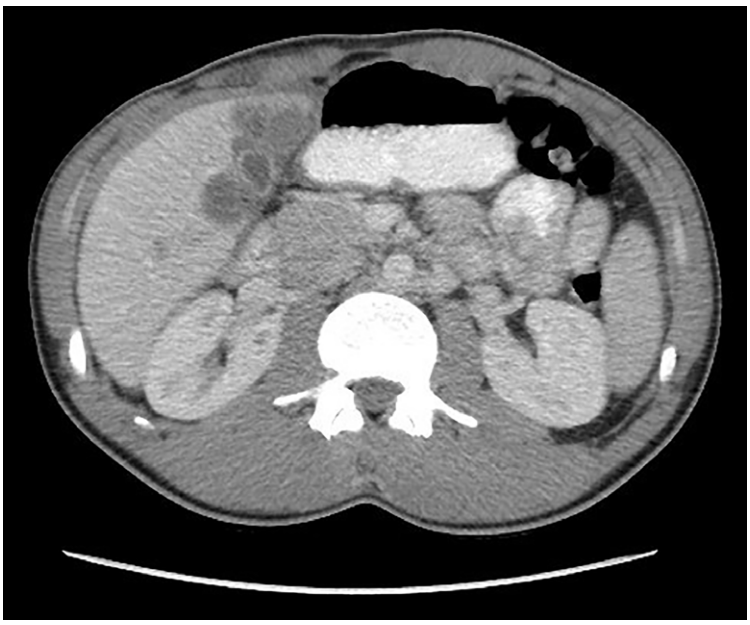

Multiple hypodense structures in the liver. What is your diagnosis?

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MINI-REVIEW

Hypotonic polyuria: at the cross-roads of copeptin

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ABSTRACT

The aetiology of hypotonic polyuria, after excluding solute diuresis, is one of primary polydipsia, central, or nephrogenic diabetes insipidus. Theoretically, these disorders should be relatively easily distinguished based on history and the results of an indirect water deprivation test. Practically, however, there is a significant overlap in diagnostic evaluation, potentially leading to an erroneous diagnosis and deleterious management plan. The ability to measure a stimulated copeptin level, either with hypertonic saline or arginine infusion, has led to greater diagnostic accuracy.

KEYWORDS

Copeptin, diagnosis, diabetes insipidus, hypotonic polyuria

INTRODUCTION

Hypotonic (urine osmolality < 800 mOsm/kg, typically < 300 mOsm/kg) polyuria (> 50 ml/kg/24 hours) is a challenging problem in clinical practice;[1,2] the differential diagnosis includes central or nephrogenic diabetes insipidus (DI) and primary polydipsia (PP), after excluding causes of solute diuresis (glucose, maltose, urea, sodium, glycine, and mannitol).[2] The incidence rate of central diabetes insipidus (CDI) is 3 to 4 per 100,000 population per year and the 5-year prevalence rate is 23 per 100,000 population, with a higher prevalence in children and older adults in a Danish cohort.[3] The incidence of X-linked nephrogenic diabetes insipidus (NDI) in the general population of Canadian provinces varied from 8.8 to 58 per million male live births for the period 1988–1997.[4] PP is present in 11-20% of chronic psychiatric patients.[5]

CDI results from the deficiency of the hormone arginine vasopressin (AVP) in the pituitary gland or the hypothalamus.[6] The severity of resulting hypotonic polyuria is dependent on the extent of neuro-hypophyseal damage, resulting in either partial (partial CDI) or complete (complete CDI) deficiency of AVP secretion.[6] NDI results from inherited or acquired resistance to AVP in the kidneys and can also be partial or complete.[7,8] CDI and NDI must be differentiated from PP, which involves excessive intake of large amounts of water despite normal

Table 1. *Laboratory parameters in hypotonic polyuria syndromes*

	Serum osmolality (mOsmol/kg H_20)	Urine osmolality (mOsmol/kg H_20)	Urine osmolality with water deprivation (mOsmol/kg H_20)	Serum vasopressin after dehydration (pg/ml)	Change in urine osmolality with desmopressin
Normal	285-295	300-900	> 800	> 2	Little or no increase
Complete CDI	< 295*	< 300, often< 200	< 300	Undetectable	Increase (> 50%)
Partial CDI	< 295*	< 300	300-800	< 1.5	Increase (> 9%)
NDI	< 295*	< 300	< 300	> 5	Increase (< 50%)
PP	< 295	< 300	> 500	< 5	Increase (< 9%)

CDI = central diabetes insipidus; NDI = nephrogenic diabetes insipidus; PP = primary polydipsia
* Serum osmolality is high if thirst/drinking is impaired) [adapted from references 10, 11].

AVP secretion and action.[5,9] Contrary to popular belief, history and clinical data may be of limited use because patients with preserved thirst mechanisms do not differ much in their laboratory parameters (see table 1).[10,11] The historical gold standard of the indirect water deprivation test to differentiate these disorders has inherent limitations that lead to difficulties with interpretation[6] and may lead to misclassification resulting in incongruous treatment and potential harm to the patient. Moving forward, a test with high diagnostic accuracy is required to classify these disorders correctly.

Clinical history and radiology

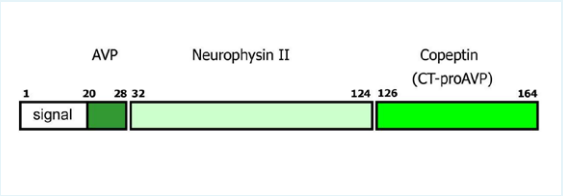
There is an overlap between the symptoms of DI and PP. Except in the rare condition of adipsic CDI, all three patient groups typically have intact or increased thirst with polyuria and polydipsia.[12,13] Traditionally, patients with CDI were thought to have a sudden onset of persistent symptoms, more nocturia, and a preference for cold beverages compared to PP patients.[14] However, in a prospective study, more than one-third of DI patients had an insidious onset of symptoms and the majority of those diagnosed with PP preferred cold beverages and had persistent symptoms.[1] The unenhanced posterior pituitary magnetic resonance imaging (MRI) was thought to be a useful investigation approach to differentiate between hypotonic polyuria subtypes. The pituitary bright spot is an area of hypersensitivity in the sagittal view on T1-weighted images, which was reported to be absent in patients with CDI in earlier studies.[15] There are conflicting case reports of a persistent bright spot in a few patients with CDI.[16] Loss of the bright spot has also been seen in congenital NDI, in approximately one-third of patients with PP, and in older adults.[1,17,18] Thus, bright spot absence is not a useful test for categorising patients correctly.

Indirect (water deprivation test) and direct AVP measurement

The diagnostic tests for hypotonic polyuria syndromes evolved after the studies on hypophysectomised dogs demonstrated a lack of anti-diuretic response with osmotic stimulation.[19] The same concept, inadequacy of urinary concentration, after water deprivation and administration of exogenous arginine vasopressin (AVP), was applied to humans with promising results.[20,21] In 1970, Miller et al. described a standardised protocol of indirect water deprivation from their analysis of 36 patients (29 with CDI, 2 with NDI, and 5 with PP) diagnosed clinically and/or by failure to respond to hypertonic saline.[10] This test was based on an indirect assessment of AVP activity by measuring urine osmolality following prolonged dehydration, and again after injection of desmopressin. Once dehydration was significant enough to induce thirst, if urine osmolality remained < 300 mOsm/kg and did not increase by > 50% after desmopressin, NDI was diagnosed. Complete CDI was diagnosed if the urine osmolality increased by > 50% after desmopressin injection. In partial CDI and PP, urine concentration increased to 300-800 mOsm/kg, with an increase of 9-50% in partial CDI and < 9% in PP after desmopressin injection. However, there was a wide overlap of urine osmolality amongst the different subgroups. Recent attempts to validate these criteria revealed an overall diagnostic accuracy of only 70% (9 of 9 patients with complete CDI, 16 of 17 patients with partial CDI, 1 of 2 patients with NDI, and 9 of 22 patients with PP).[14] The reason for failure of the indirect water deprivation test is multifactorial and includes small patient numbers which were used to establish reference values, weak vasopressin stimulation in some patients secondary to failure to achieve a hyperosmolar serum, and renal pathophysiology. Chronic polyuria can cause washout of the renal medullary concentration gradient and downregulate aquaporin-2 (AQP2) channels resulting in loss of urinary concentration ability in CDI and PP.[22-24] However, AVP-V2 receptors may be up-regulated in chronic partial CDI, increasing anti-diuretic response to low levels of AVP.[25,26] The result of these opposing mechanisms is a convergence of distinct underlying disorders to a near-identical urinary phenotype. Moreover, in NDI there may be only partial resistance to AVP and clinical resemblance to partial CDI.[27,28] Thus, it becomes difficult to differentiate amongst these conditions exclusively based on the water deprivation test.

In a seminal paper, both direct AVP measurements after osmotic stimulation and standard indirect water deprivation test correctly identified severe CDI, but discrepant results were seen in patients with PP.[29] Of

Figure 1. *Cartoon of the 164-amino acid peptide precursor, preprovasopressin. This figure shows the signal sequence (white), AVP (dark green), neurophysin II (pale green), and copeptin (light green). Copeptin (CT-proAVP) is the C-terminal part of proAVP. Numbers indicate amino acids of the human protein.*



AVP = arginine vasopressin; CT-proAVP = C-terminal proAVP; signal = signal peptide. (Adapted from Nickel et al: The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Medicine 2012 10:7. Open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0).[37]

the 10 patients who appeared to have PP by the indirect test, three had unequivocal evidence of AVP deficiency by direct measurement. This was further corroborated by a uniformly excellent response to desmopressin therapy. In another study of 50 patients with polyuria-polydipsia syndrome, direct AVP measurements showed a dismal diagnostic accuracy of around 38% (2 of 9 patients with complete CDI, 5 of 17 patients with partial CDI, 16 of 22 patients with PP, and neither of 2 patients with NDI were diagnosed correctly). The authors concluded that plasma AVP levels were not reliable for distinguishing PP and CDI, particularly the partial form of CDI.[12] The problems of high pre-analytical instability of commercial AVP assays, lack of a comparative diagnostic gold standard, and paucity of a defined normal AVP response to osmolality makes AVP measurements a non-reliable test in current clinical practice.[30-32]

Copeptin: biochemistry, physiology, and measurement

Copeptin, first discovered in 1972 from the posterior pituitary of pigs, originates from the precursor pre-pro-vasopressin with AVP and neurophysin II (figure 1).[33-37] It is a 39 amino acid glycosylated peptide with a leucine-rich core that is thought to modulate the three-dimensional unfolding of vasopressin into a functioning molecule.[38] AVP measurement is technically difficult due to AVP instability, high in vitro thermolability, and a short half-life of 10-44 minutes; copeptin has a half-life of approximately 86 minutes, high ex vivo stability, and is easy to measure. Copeptin is stable in EDTA plasma and serum for seven days at room temperature and 14 days at 4 °C, allowing for delayed analysis.[36] Reliable results are available rapidly from a small volume of plasma or serum (50 µl) using either a manual sandwich immunoluminometric assay (LIA) or a less complicated commercially available automated immunofluorescent (KRYPTOR) test for a reasonable price, without the need for pre-analytical laboratory processes.[39-41]

The stimuli for copeptin mimic those for AVP with similar release kinetics in response to changes in osmotic pressure (correlation coefficient 0.94) and low arterial blood volume/pressure.[42-44] Given the equimolar 1:1 ratio between the two peptides, copeptin can serve as a surrogate for AVP.[36,43] The plasma copeptin concentration in health ranges from 1.0-13.8 pmol/l (median: 4.2 pmol/l) in adults[36] and 2.4-8.6 pmol/l (mean 5.2 ±1.56 pmol/l) in children.[45] Renal clearance is responsible for partial elimination of copeptin but is not the main determinant of its concentration.[46,47] Females tend to have lower values, but median values are comparable across age groups.[36,48] Increase in copeptin levels has been observed during fasting, post-exercise, and psychological stress, while levels significantly decreased after small amounts of water ingestion.[43,49-51] Variability was not observed in response to the menstrual cycle but there does appear to be a minor impact of circadian rhythm in some patients.[52,53] Copeptin has also been studied as a biomarker for various stress states like ischemic stroke, septic shock, traumatic brain injury, lower respiratory tract infections, and myocardial infarction.[36,39]

Copeptin: an evidence-based journey in the differentiation of hypotonic polyuria subtypes

Over the last decade, copeptin has replaced plasma vasopressin due to its stability and is now an important test in hypotonic polyuria work up. In a pioneering prospective study of 50 patients with hypotonic polyuria and 20 healthy subjects, plasma AVP and copeptin levels were measured after a standard water deprivation test.[14] In case of discrepancy between direct and indirect test results, reference diagnosis was established based on medical history, clinical findings, and therapeutic response to desmopressin. The osmotically-stimulated copeptin was found to have an overall diagnostic accuracy of 83%. Baseline copeptin values greater than 20 pmol/l identified patients with NDI, and concentrations below 2.6 pmol/l indicated complete CDI. The ratio of copeptin increase during an 8-hour dehydration period to the serum sodium concentration measured after 16 hours of water deprivation increased the diagnostic yield to 94% (sensitivity 86% and specificity 100%) in discerning patients with PP from partial CDI. The major limitation of this study and with others is the relatively small patient numbers and lack of a true gold standard test with which the copeptin results could have been compared.

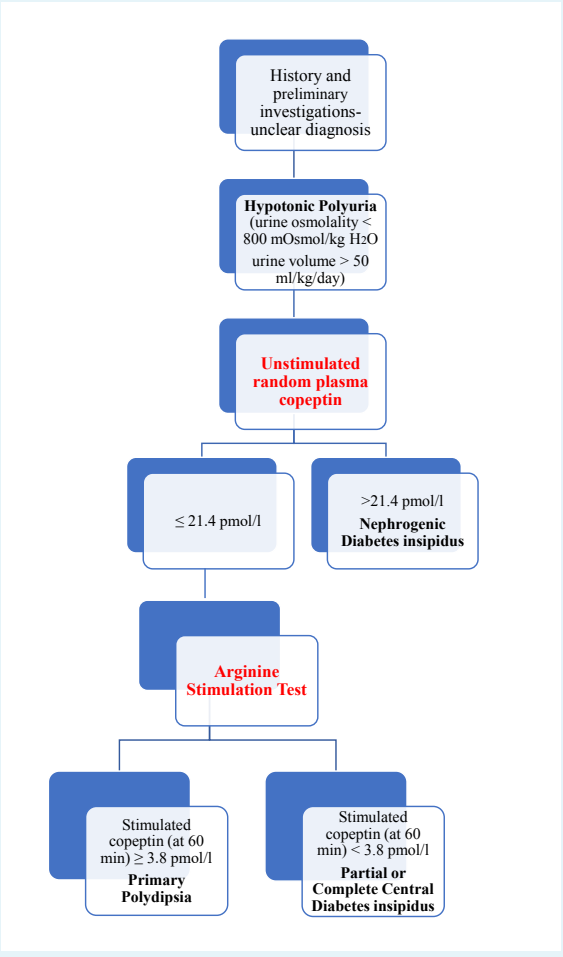
A prospective multicentre observational cohort study of 55 patients with the history of polyuria and polydipsia evaluated the accuracy of copeptin.[54] A standardised combined water deprivation and a 3% saline infusion test were performed. Water deprivation started at 08.00 hours (h) as long as plasma sodium did not exceed 147 mmol/l and continued until the plasma sodium surpassed that value. Once plasma sodium was greater than 147 mmol/l, if urine osmolality was less than 300 mmol/l, desmopressin was given. If plasma sodium did not exceed 147 mmol/l by 13.00 h, hypertonic saline was administered. A single baseline copeptin level > 21.4 pmol/l (without prior fluid restriction) differentiated NDI from other aetiologies with a 100% sensitivity and specificity, rendering water deprivation unnecessary in these patients. An osmotically-stimulated copeptin ≥ 4.9 pmol/l (at sodium levels > 147 mmol/l) differentiated between patients with PP and patients with partial CDI with sensitivity and specificity of 94%. The specificity further improved to 96% when complete CDI patients were included in the analysis. AVP measurements performed poorly for differentiation between partial CDI and PP yielding a definite diagnosis of PP in only 44% of patients with this entity.

In a landmark multicentric study of 156 hypotonic polyuria patients, both indirect water deprivation and hypertonic saline infusion tests were performed on separate days.[1] In the latter test, plasma copeptin was measured when the plasma sodium level had increased to at least 150 mmol/l. In the absence of a gold standard, the diagnosis was determined at study completion by two endocrinologists based on available history and laboratory data without knowledge of the copeptin levels. The overall diagnostic accuracy in distinguishing patients with PP from CDI with hypertonic saline infusion test was 96.5% (sensitivity 93%, specificity 100%) with a predefined copeptin level of > 4.9 pmol/l compared to 76.5% (sensitivity 86.4%, specificity 69.5%) with the indirect water deprivation test. Increasing the predefined copeptin level to > 6.5 pmol/l increased sensitivity further without compromising specificity. The hypertonic saline infusion test was also more accurate in correctly distinguishing PP from partial CDI, compared to the indirect water-deprivation test ($p < 0.001$). Adding water deprivation plasma copeptin ratios did not improve the diagnostic accuracy of the indirect water deprivation test in distinguishing PP from CDI, as had been demonstrated in a previous study. The proposed morning copeptin level of < 2.6 pmol/l after an overnight water deprivation to identify patients with complete CDI had a diagnostic accuracy of only 78%. All three patients with NDI had a copeptin level of > 21.4 pmol/l. The investigators concluded that hypertonic saline-stimulated copeptin measurement was superior to the indirect water deprivation test in distinguishing CDI from PP. However, the hypertonic saline infusion was associated with more side effects and required close monitoring of sodium levels to achieve an increase in plasma sodium concentration within the hyperosmotic range followed by a rapid reversal to a safe value.

For this reason, arginine infusion, which is known to stimulate the release of anterior pituitary hormones, was explored as an easier and safer way to stimulate copeptin without inducing hypernatraemia. The copeptin response to arginine was compared with the final diagnosis for hypotonic polyuria based on the results of indirect water deprivation test, patient characteristics, and treatment response in prospective study design.[55] Patients with NDI identified based on a single baseline copeptin value (as defined by previous studies) were excluded from the study protocol. The arginine stimulation test (arginine infusion over 30 minutes) was assessed in development and validation cohorts of patients with CDI (21 in the development cohort, 19 in the validation cohort) or PP (31 in the development cohort, 27 in the validation cohort). The comparator cohort included 50 healthy adults (20 in the development cohort, 30 in the validation cohort) and 42 children (who had suspected growth hormone deficiency) in the development cohort. Arginine infusion increased copeptin concentrations 2.2 times in patients with PP, 1.2 times in the patients with CDI, and 1.5-1.8 times in the healthy control cohort. In the pooled dataset, an arginine-stimulated copeptin cut-off of 3.8 pmol/l measured at 60 minutes was associated with a diagnostic accuracy of 93% (sensitivity 93% and specificity 92%) and 90% (sensitivity 93% and specificity 88%) in differentiating between CDI and PP, and between partial CDI and PP, respectively. Moreover, the copeptin response was not associated with other clinical and biochemical variables in their post-hoc analysis.

Post-hoc head-to-head comparison of 60 patients (23 with DI, 37 with PP) between arginine-stimulated vs hypertonic saline-stimulated copeptin response revealed their diagnostic accuracies as 93% and 100%, respectively, in distinguishing between patients with DI and PP. However,

Figure 2. *A proposed simplified approach to hypotonic polyuria. (Copeptin cut-off of 3.8 pM at 60 minutes after arginine stimulation had a diagnostic accuracy of 93% for differentiating between DI and PP (possible limitations being thirst, nausea).*[55]



the arginine-stimulated protocol had fewer adverse effects (less than 5%) with arginine stimulation (including two participants with vomiting who were not included in the main dataset) compared to > 70% with hypertonic saline) with a significantly lower test burden. This short, practical, and relatively safe arginine-stimulated copeptin response could become the new standard test for the workup of hypotonic polyuria when the diagnosis is unclear from initial history and laboratory investigations (figure 2). The results of the CARGOx study when available (use of copeptin measurement after arginine infusion for the differential diagnosis of diabetes insipidus, NCT03572166) will be helpful in this regard.

CONCLUSION

The differential diagnosis of hypotonic polyuria is challenging, especially distinguishing partial DI from PP. The current diagnostic standard of the indirect water deprivation test has several limitations, including a long test duration and poor diagnostic accuracy especially in distinguishing partial DI and PP. Over the past decade, copeptin has emerged as a biomarker for various disorders. Plasma copeptin levels are highly correlated with AVP; high baseline values correctly identify patients with NDI. For differentiating PP from CDI, hypertonic saline stimulated copeptin level of > 4.9 pmol/l had a higher diagnostic accuracy than the water deprivation test. The arginine-stimulated copeptin response circumvents the shortcomings of the hypertonic saline test (longer test duration, more side effects) and provides a novel, pragmatic, and safe work-up approach to diagnose hypotonic polyuria syndromes.

DISCLOSURES

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ORIGINAL ARTICLE

Severe acute respiratory infections surveillance for early signals in the community

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ABSTRACT

Background: Surveillance of acute respiratory infections (ARI) in the Netherlands and other European countries is based mostly on primary care data, with little insight into the severe spectrum of the disease. We compared time-trends for ARI in secondary care with influenza-like illness (ILI), ARI and pneumonia in primary care, and crude mortality, in order to assess the value of routinely collected data on respiratory infections in hospitals and the added value of severe acute respiratory infections (SARI) surveillance. Methods: We calculated incidence of ARI in secondary care, ILI, ARI, and pneumonia in primary care, and crude mortality using five historical databases (2008-2016). Results: Over eight years, seasonal incidence peaks of ARI in secondary care occurred earlier than ILI and ARI incidence peaks in primary care, except during the 2009 influenza A(H1N1) pandemic and post-pandemic season. The median time-lag between ARI in secondary care and ILI, ARI and pneumonia in primary care was 6.5 weeks, 7 weeks, and 1 week, respectively. Crude mortality lagged a median 5 weeks behind ARI in secondary care. Conclusion: This observational study demonstrates that routinely collected data can be used for describing trends of ARI in secondary care and may be suitable for near real-time SARI surveillance. In most seasons, the incidence peaks for ARI in secondary care preceded the peaks in primary care and crude mortality with a considerable time-lag. It would be of great value to add microbiological test results to the incidence data to better explain the difference in time-lag between these surveillance systems.

KEYWORDS

Acute respiratory infections in secondary care, crude mortality, primary care consultations, severe acute respiratory infections

INTRODUCTION

Most European countries, including the Netherlands, have a well-established near real-time (weekly) surveillance system for influenza-like illness (ILI) or other acute respiratory infections (ARI) in primary care. In contrast, real-time surveillance data about severe acute respiratory infections (SARI), i.e., patients requiring hospital admission, is rarely available. The limited historic and real-time data on severe respiratory infections requiring hospitalisation became recently apparent during the severe 2017/2018 influenza epidemic in the Netherlands.[1]
During the 2017/2018 winter season, broad media attention was generated on hospitals that were overwhelmed by patients with influenza virus infections.[2] These media reports reflected the severity of the influenza epidemic that resulted in shortages in bed capacity and medical staffing. This could not be confirmed by surveillance data because a national representative SARI surveillance system is currently unavailable.[1] In addition, the ongoing COVID-19 pandemic also shows the importance of real-time syndromic surveillance data for early detection of signals that require further investigation. Surveillance is a vital tool to monitor shifts in the occurrence and burden of infections and diseases in the population.[3,4] Assessing the severity of an influenza epidemic in time, place, and person is essential to guide

control activities, to assess the impact on healthcare systems, and to guide communication with the public and the media. In the Netherlands in primary care, weekly surveillance of ILI by sentinel general practitioners (GPs) was established in 1970 and virological test results were added in 1992, providing robust longitudinal data on incidence of ILI and influenza virus infection in the general practice population. The Dutch mortality monitoring system provides data on the total number of deaths from all causes, stratified by age group and region, with a weekly analysis of excess mortality.[5] It is a near real-time surveillance system, but the weekly mortality data are not disease-specific. The Dutch respiratory surveillance pyramid summarises these surveillance systems at different levels of care (figure 1). In the Dutch healthcare system, the GPs have a gatekeeping role for referral to specialised care.

SARI surveillance has been the missing link in the existing respiratory infections surveillance systems in the Netherlands. The Dutch Hospital Data (DHD) is a national register of hospital discharge diagnoses using International Statistical Classification of Diseases and Related Health Problems (ICD) codes.[6] However, it is available with a one-year time-lag and therefore not suitable for real-time surveillance. In 2015, a pilot study by the National Institute for Public Health and the Environment (RIVM) started in two hospitals, Leiden University Medical Center (LUMC) and Jeroen Bosch Hospital (JBH), with the main objective to set up SARI surveillance.[7,8] As part of this pilot study, historical SARI data from LUMC were made available for analysis in the current study, aiming to assess the value of routinely collected data on respiratory infections in hospitals and the added value of SARI surveillance. Positioning SARI surveillance in relation to other existing respiratory surveillance data is important to interpret the potential added value of SARI surveillance.

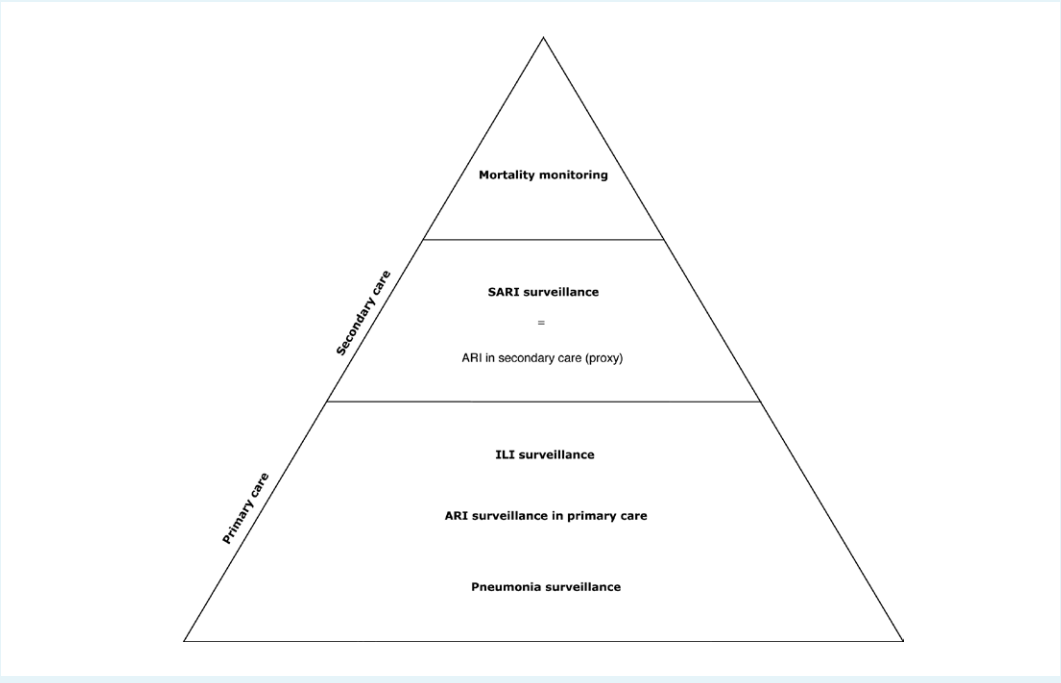
MATERIALS AND METHODS

ARI in secondary care database

Data on patients with an ARI receiving specialist care during the period between week 40 of 2008 and week 20 of 2016 were provided by the LUMC, a 585-bed tertiary university teaching hospital in Leiden, province of South Holland, the Netherlands.

Patients with ARI were defined as those consulting the LUMC Emergency Department (ED) or outpatient clinic who were registered with diagnostic codes corresponding to a respiratory tract infection (RTI). These codes were based on the Dutch financial coding system, applied by the national Dutch Healthcare Authority (NZa), and used by all healthcare facilities in the Netherlands.[8] Depending on ARI severity, these patients were admitted to an intensive care unit (ICU) or regular ward or discharged for treatment

Figure 1. *The respiratory surveillance pyramid in the Netherlands*



at home. Patients discharged without admission do not completely fulfil the World Health Organization (WHO) SARI case definition,[9] and we were unable to distinguish outpatients from admitted patients. Therefore, we used 'ARI in secondary care' as a proxy for SARI. The database included consultation date, gender, and ward of admission (ICU/non-ICU),[8] but not microbiological data.

The Dutch Medical Research Involving Human Subjects Act did not apply to this study, because only fully anonymous data were used and there were no interventions other than routine clinical care. A waiver for full medical ethical review was obtained from the Medical Ethical Committee of the University Medical Center Utrecht (reference number WAG/om/15/034147).

Primary care databases

Influenza-like illness

Data from the Sentinel Practices of NIVEL Primary Care Database were used to calculate the incidence of ILI in primary care from week 40 of 2008 to week 20 of 2016.[10] The participating GP practices (39 practices with 60 GPs) report on the weekly number of patients consulting them for ILI, which is defined as 1) sudden onset of symptoms, 2) fever, and 3) at least one of the following symptoms: cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain, or myalgia.[11] The population covered by this sentinel network is approximately 0.7% (124,000 patients) of the Dutch population (17.2 million) and is representative for age, gender, regional distribution (Supplementary file*, figure 1), and population density.[11] In the Netherlands, an influenza epidemic is declared if the incidence of ILI in primary care is above the threshold of 5.1 per 10,000 persons per week for at least two consecutive weeks in combination with the detection of influenza virus in combined nasal and throat swabs from a selection of these ILI patients.[1]

Acute respiratory infections in primary care

Data on patients consulting a GP for acute respiratory infection (e.g., sinusitis, laryngitis, bronchitis, or influenza) were obtained from the Nivel Primary Care Database from week 40 of 2009 until week 20 of 2016. ARI in primary care is less specific for influenza virus infection than ILI, but seasonal estimates are highly correlated.

Pneumonia in primary care

Data on patients consulting a GP for pneumonia were also obtained from the Nivel Primary Care Database from week 40 of 2009 to week 20 of 2016. Pneumonia in primary care is diagnosed by the GP mostly on clinical judgement. The sentinel network for ARI and pneumonia in primary care consists of 419 GPs, covering approximately 10% (1.7 million) of the Dutch population.[12]

Crude mortality monitoring

Deaths are recorded by municipalities and then reported to Statistics Netherlands.[13] During the 2009 influenza pandemic, RIVM and Statistics Netherlands initiated a weekly monitoring system for crude mortality. It monitors the total reported number of deaths from all causes, stratified by age group and region. The presence of excess mortality is verified and reported weekly.[5] For our observational study, all-cause mortality data were collected from Statistics Netherlands for the province of South Holland, the Netherlands, with over 3.6 million persons in the period from week 1 of 2009 though week 20 in 2016.[14] Provincial data were used because it was not feasible to obtain crude mortality data for the LUMC catchment population.

Statistical analysis

Definitions and calculations

Data are presented for both the 'respiratory year' and 'respiratory season', defined respectively as the period from week 40 through week 39 of the following year, and the period from week 40 through week 20 the following year. Data for 2015/2016 are limited to the respiratory season (week 40 of 2015 through week 20 of 2016). The incidence for ARI in secondary care was calculated as the number of patients consulting the hospital per week, divided by the total number of persons in the LUMC catchment population (182,704), and expressed per 10,000 persons (Supplementary file*, figure 2). A hospital catchment population is defined as the median number of persons who would attend the hospital where they would require treatment.[15] The catchment population was calculated by dividing the total number of hospitalisations due to RTI in the LUMC by the total number of hospitalisations due to RTI in the Netherlands and multiplying this proportion by the total Dutch population size. The data required for the calculation of the catchment population was provided by Dutch Hospital Data.[6] A selection of WHO ICD-10 codes related to RTI (J00-J22, A15, A16, A48.1, A70, and A78) was determined for the LUMC for the years 2014 through 2016. These years were selected because they reflected the most up-to-date situation at the time of the study. Taking into account the non-normal distribution of the catchment population over the years 2014 through 2016, we used the median value for our incidence calculations.

The ILI incidence in primary care was calculated as the number of ILI patients consulting the GP per week, divided by the total number of patients registered in the participating practices, and expressed per 10,000 persons. The ARI incidence in primary care and pneumonia in primary care are calculated in the same way from the larger Nivel Primary Care Database. The crude mortality in the province of South Holland, the Netherlands, was

calculated as the number of deceased patients, divided by the total population of the province of South-Holland and expressed per 10,000 persons. It is important to note that crude mortality was used only for comparing trends, as it reflected a larger population than the LUMC catchment population. Therefore, the magnitude of all-cause mortality per week was not relevant to this study.

Measures of disease frequency

Descriptive statistics were used to compare trends in ARI in secondary care, ILI, ARI and pneumonia in primary care, and crude mortality, including three-week moving average incidences and peak incidence. The peak incidence per season for ARI in secondary care, ILI, ARI, and pneumonia in primary care, and crude mortality was defined as the highest incidence in a season. Three-week moving averages are used to smooth out the trend by filtering out 'noise' from weekly incidence fluctuations. The time-lag between respiratory surveillance systems was defined as the number of weeks between incidence peaks, relative to ARI in secondary care. Median and interquartile range (IQR) were used to describe these time-lags. Statistical differences between time-lags were calculated using the Kruskal Wallis test. Statistical analysis was performed using SPSS (version 22) and Excel (version 2010).

RESULTS

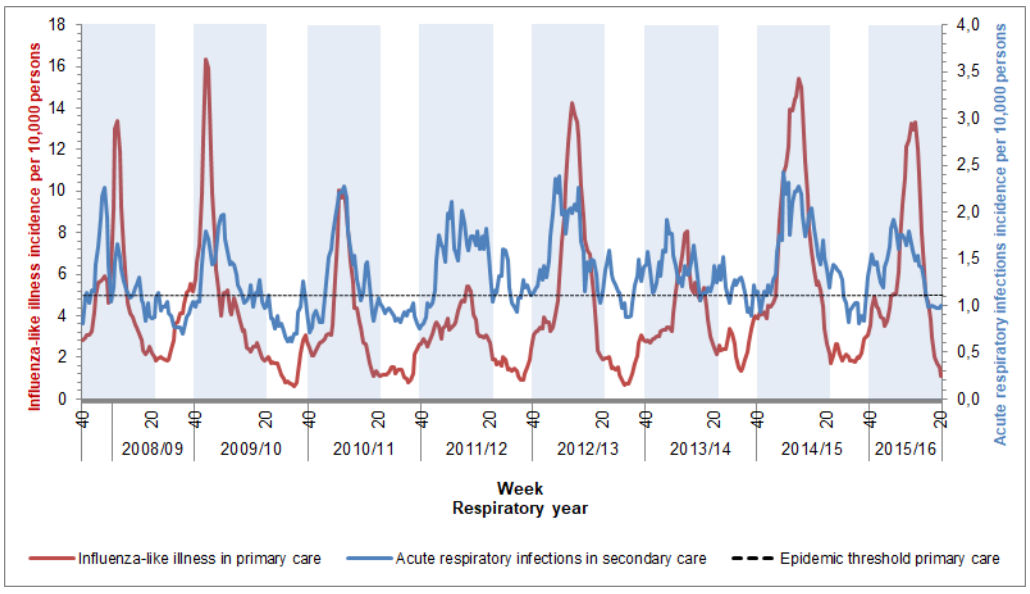
ILI in primary care versus hospital consultations

Three-week moving incidence averages of ARI in secondary care and ILI in primary care showed clear peaks during the respiratory season. On visual inspection of the time series, elevations of ARI in secondary care appear broader than for ILI (figure 2).

High ILI incidence was confined to the respiratory season (e.g., week 40 through week 20 the following year), whereas ARI incidence in secondary care showed a more diverse pattern, with clear peaks more frequent in winter, but not entirely restricted to the respiratory season.

The highest peak in weekly incidence for ARI in secondary care was 3.9 cases/10,000 persons (week 1 of 2015), and peak ILI incidence was 19.1 cases/10,000 persons (week 46 of 2009) (Supplemental file*, table 1). The ARI peaks in secondary care generally occurred earlier than the ILI peaks in primary care, except during the influenza pandemic season of 2009/2010 and the post-pandemic season of 2010/2011. Overall, the median time-lag between ARI in secondary care and ILI peaks was 6.5 weeks (IQR 0-9 weeks). No statistical difference was found with regard to time-lags between respiratory seasons (Kruskal Wallis test; p = 0.4). During the six seasons in which ARI peaked

Figure 2. *Three-week moving average incidence of influenza-like illness in primary care and acute respiratory infection in secondary care (2008-2016)*



*The epidemic threshold was 5.1 cases per 10,000 persons and was based on primary care data.[16]
**Blue shading depicts the respiratory season (week 40 through week 20 the following year).

before ILI, the median time-lag was eight weeks (IQR 6-9 weeks) (Kruskal Wallis test; p = 0.4).

ARI in primary care versus hospital consultations

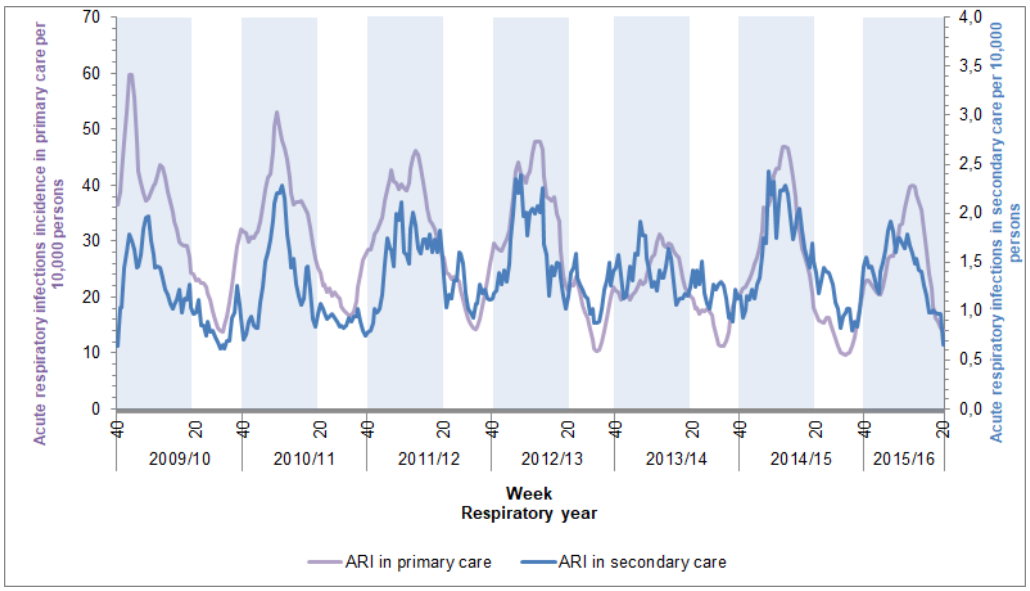
ARI in primary care showed similar broader peaks, when compared to ARI in secondary care (figure 3). The ARI peaks in secondary care preceded ARI in primary care during six respiratory seasons, except during 2009/2010 and 2010/11 (table 1). The median time-lag between ARI in secondary and primary care was seven weeks (IQR -4-9), but differences between respiratory seasons were not significant (Kruskal Wallis test; p = 0.4).

Table 1. *Incidence peak, peak week, and time-lag for acute respiratory infections in secondary care, influenza-like illness in primary care, ARI in primary care, pneumonia in primary care, and crude mortality in the period 2008-2016.*

Respiratory year	Dataset†	Peak (week number)	Time-lag relative to ARI (weeks)	Peak incidence†
2008/2009	ARI-1*	50	5	2.46
	ILI	3		14.14
	ARI-2**	n.a.	n.a.	n.a.
	Pneumonia§	n.a.		n.a.
	MOR	3	5	
2009/2010	ARI-1	52	-6	2.13
	ILI	46		19.07
	ARI-2	46	-6	64.35
	Pneumonia	1	2	5.08
	MOR	3	4	
2010/2011	ARI-1	5	-2	2.46
	ILI	3		11.34
	ARI-2	1	-4	55.47
	Pneumonia	1	-4	6.3
	MOR	1	-4	
2011/2012	ARI-1	1	9	2.90
	ILI	10		7.42
	ARI-2	8	7	46.78
	Pneumonia	2	1	6.95
	MOR	8	7	
2012/2013	ARI-1	51		2.74
	ILI	5	6	16.23
	ARI-2	8	9	50.28
	Pneumonia	51	0	6.88
	MOR	5	6	
2013/2014	ARI-1	49	10	2.19
	ILI	7		8.98
	ARI-2	6	9	31.82
	Pneumonia	2	5	4.50
	MOR	2	5	
2014/2015	ARI-1	1	7	3.94
	ILI	8		16.12
	ARI-2	7	6	49.24
	Pneumonia	2	1	7.42
	MOR	3	2	
2015/2016	ARI-1	51	9	2.30
	ILI	7		14.81
	ARI-2	7	9	41.54
	Pneumonia	6	8	5.95
	MOR	8	10	

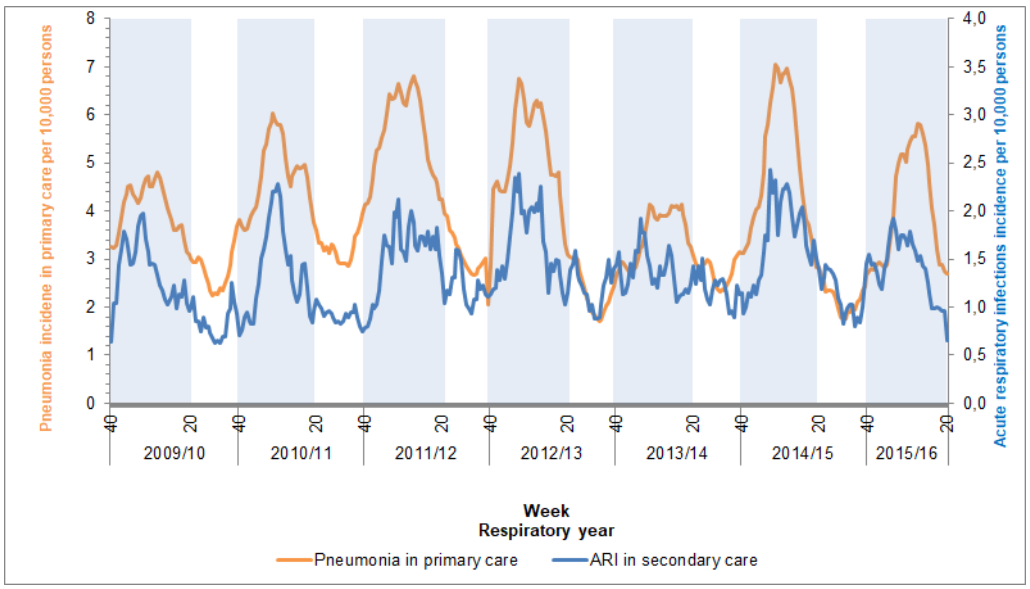
* ARI-1: acute respiratory infections in secondary care; ** ARI-2: acute respiratory infections in primary care; ILI = influenza-like illness in primary care; MOR = crude mortality; n.a. = not applicable; § Pneumonia = pneumonia in primary care; † incidence per 10,000 persons

Figure 3. *Three-week moving average of incidence of acute respiratory infections in primary care and acute respiratory infections in secondary care (2009-2016)*



* Blue shading depicts the respiratory season (week 40 through week 20 the following year).

Figure 4. *Three-week moving average of incidence of pneumonia in primary care and acute respiratory infections in secondary care (2009-2016)*



*Blue shading depicts the respiratory season (week 40 through week 20 the following year).

Pneumonia in primary care versus hospital consultations

On visual inspection, time trends of pneumonia in primary care appear to have a similar pattern as ARI in secondary care (figure 4). The ARI peaks in secondary care preceded pneumonia peaks in primary care with a median time-lag of one week (IQR 0-5) (Kruskal Wallis test; p = 0.4). In respiratory season 2012/2013, the peaks of ARI in secondary care and pneumonia in primary care occurred in the same week (week 51 of 2012).

Crude mortality versus hospital consultations

Mortality in the province of South Holland, the Netherlands, as well as ARI in secondary care show winter peaks in the respiratory season. However, crude mortality elevations appear broader with less well-defined peaks than ARI elevations (figure 5.). Overall, the crude mortality peak lagged a median five weeks behind the ARI peak (IQR 3-7 weeks) (Kruskal Wallis test; p = 0.4).

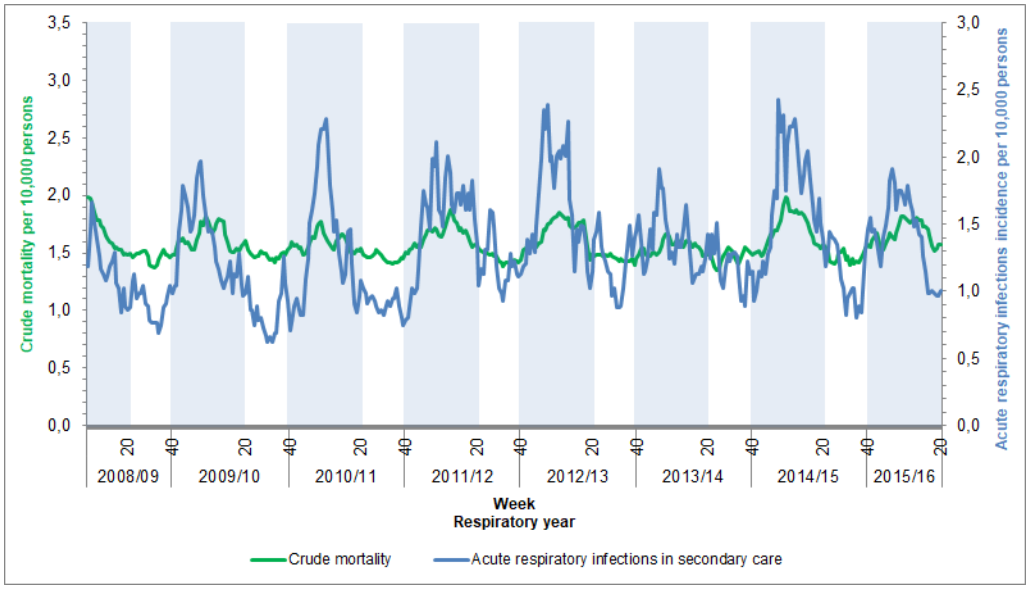
DISCUSSION

This observational study demonstrates that routinely collected data can be used for describing trends of ARI in secondary care and may be suitable for near real-time SARI surveillance. We show that ARI incidence in secondary care peaked earlier than ILI, ARI incidence in primary care, and crude mortality with a considerable time-lag. Pneumonia in primary care had a shorter time-lag, only one week behind ARI in secondary care.

Routinely collected data on respiratory infections

Our principal finding that ARI in secondary care peaks before ILI, ARI, or pneumonia in primary care in most respiratory seasons could be explained by high-risk patient groups. We hypothesise that hospitalisations for ARI early in the respiratory season largely consists of high-risk elderly patients with comorbidities or young children. Young children could also be responsible for the earlier peak because of hospital admissions for respiratory syncytial virus infection.[17] In addition, as in many European countries, the Dutch population is ageing, and elderly patients with comorbidities increasingly live at home.[18,19] This frail, high-risk patient group is associated with an increased demand for hospital admissions.[20-22] In other words, this high-risk group is likely to be referred to, and subsequently admitted to, the hospital earlier because of respiratory infections than relatively healthy persons. In most seasons, this demand could be reflected in an earlier incidence peak for ARI in secondary care compared to the incidence peak for ILI, ARI, and pneumonia in primary care. Only for the pandemic and post-pandemic

Figure 5. *Three-week moving average of incidence of crude mortality and acute respiratory infections in secondary care (2008-2016)*



* Blue shading depicts the respiratory season (week 40 through week 20 the following year).

seasons did we find an inverted time-lag for ILI and ARI in primary care, which is difficult to explain without additional data on co-morbidities and microbiological test results. However, a disproportionately higher ARI incidence in the younger age groups versus older age groups is likely to play a role.[23,24]

Pneumonia in primary care might be the best proxy for ARI in secondary care, because it has shortest median lag-time with ARI in secondary care compared to the other surveillance systems. An explanation of this finding could be that patients diagnosed and treated for CAP in primary care by their GP are most likely to be referred to a hospital if the antibiotics do not have the expected effect.

ARI incidence in secondary care and crude mortality showed similar trends, with peaks in winter over a period of eight respiratory years. The seasonality of crude mortality has been clearly documented and is primarily caused by increase in deaths in the elderly during winter.[25,26] Van Asten et al. stated that winter peaks of all-cause mortality are often largely attributed to influenza and sometimes cold snaps, but other pathogens, such as respiratory syncytial virus, parainfluenza, and norovirus, may also play a substantial role in the mortality of the elderly.[27]

Our results are consistent with another Dutch study in which respiratory ICU admissions[28] were compared with ILI incidence in primary care from 2007-2015.[29] Its data indicate that in six of the nine seasons studied, increase in respiratory ICU admissions preceded ILI trends with a median time-lag of one week. In contrast to our results, a German study by Buda et al. found that the trend of SARI peaks closely matched the peaks for respiratory infections in primary care in the influenza seasons 2012-2016.[30] Comparison with our study is difficult because of large differences in methodology and healthcare systems. SARI surveillance in Germany is based on ICD-10 codes related to SARI and the catchment population is not reported, which make incidence calculation and comparisons with our study impossible. In contrast to the German healthcare system, GPs have a gatekeeper role in the Dutch healthcare system and control, to a large degree, which patients are referred to the hospital.

Value of SARI surveillance

The finding that ARI incidence in secondary care peaks before ILI, ARI, or pneumonia in primary care in most respiratory seasons is important for SARI surveillance in terms of preparedness and emergency response.[31,32] Timeliness is critical for detecting outbreaks and taking required public health action to reduce their size, ultimately leading to lower morbidity and mortality.[31,33] For example, in a retrospective analysis, several clusters of hospital admissions for ARI were identified that occurred in 2005 to 2007, and earlier than the recorded Q-fever outbreaks in the Netherlands.[34] In hindsight, a well-functioning SARI surveillance system might have led to earlier detection, and possibly earlier healthcare interventions, such as the treatment and follow-up of acute Q-fever patients, and implementing veterinary control measures. During the severe 2017/2018 influenza epidemic, a robust SARI surveillance system could have provided a timelier insight into the heavy burden on hospitals. This could have led to more timely healthcare measures, such as cohort isolation or the implementation of influenza point-of-care testing at the emergency department to improve patient flow.

The value of real-time SARI surveillance could be different between years, because SARI incidence is dependent on the severity of the respiratory year. In turn, the severity of the respiratory year is variable, depending on the type of circulating seasonal pathogen(s) and characteristics of patients most severely affected. We cannot draw conclusions on the predictive value of SARI surveillance, because this study is merely a descriptive study based on retrospective data. However, our results confirm the need for SARI surveillance data in the timely detection of future outbreaks and indicate that we cannot depend solely on primary care data.

Limitations

First, the absence of microbiological diagnostic results is an important barrier to interpreting incidence differences between ARI in secondary care, primary care consultations, and crude mortality. Data on microbiological test results would be needed to explain the whole spectrum of respiratory infections and to better understand the time-lag between the surveillance systems per season. For example, the influenza-related SARI could be more accurately defined and make comparisons with ILI more biologically plausible. Together with data on medical history, such as co-morbidities and place of residence, it could clarify which patient group is primarily reflected in the peak of ARI incidence in secondary care. In the setting of SARI surveillance, detection of causative pathogens is crucial in mitigating the effect of disease outbreaks by taking timely health care interventions.[35-37] Other causative pathogens associated with influenza, and with high morbidity and mortality, could be added to the SARI surveillance system, such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Aspergillus* spp (invasive pulmonary aspergillosis). High-quality SARI surveillance with laboratory-confirmed outcomes could also monitor the impact of vaccines and target healthcare interventions on specific risk groups.

A second limitation is that we used retrospective data to describe trends. Robust 'real-time' SARI-surveillance data are not yet available in the Netherlands. Third, incidence calculations for ARI in secondary care were based on one

hospital in the western part of the Netherlands. Including only a tertiary hospital could have led to selection bias because these types of hospitals tend to have a different patient population than general hospitals. However, long-term historical data from other hospitals were not available to us. Fourth, by using province-based mortality data instead of catchment area-based data, our mortality calculations might have been overestimated to some extent. A possible explanation could be that the province-based mortality data included the city of Rotterdam, whose inhabitants are known to have lower life expectancy than the general Dutch population.[38] Finally, this study used 'acute respiratory infections in secondary care' as a proxy for SARI patients because no distinction could be made between patients admitted to the hospital, reviewed at the outpatient clinic, or discharged home. This could have led to overestimation of incidence calculations.

CONCLUSION

This observational study demonstrates that routinely collected data can be used for describing trends of ARI in secondary care and may be suitable for near real-time SARI surveillance. The principal finding is that in most seasons, the incidence peaks for ARI in secondary care preceded the peaks in primary care and crude mortality with a considerable time-lag. This is relevant information for preparedness and emergency control. It would be of great value to add microbiological test results to the incidence data to better explain the difference in time-lag between these surveillance systems.

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DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

*Supplementary materials are available from the authors upon request.

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ORIGINAL ARTICLE

Implementation of 'Choosing Wisely Netherlands' for internal medicine

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ABSTRACT

Background. The Choosing Wisely campaign aims to reduce low-value care to improve quality and lower healthcare costs. Our objective was to determine the current implementation of the Choosing Wisely Netherlands campaign and the 10 recommendations (released in 2014) for internal medicine.

Methods. We actively surveyed physicians and residents in the departments of internal medicine in 13 hospitals in the Netherlands. The survey was performed during a presentation about Choosing Wisely and we asked whether they thought that the recommendations were implemented.

Results. Between May and November 2018, we surveyed 281 physicians and residents, of which we received 2625 answers (response rate 85%). We found that 178 (68.5%) of 260 physicians were unaware of the Choosing Wisely campaign. For the implementation of recommendations, 1506 (75.2%) of 2003 answers stated that physicians applied the recommendations in clinical practice. We found no differences in implementation of physicians who were aware or unaware of the campaign, respectively 529 (76.1%) of 695 versus 854 (74.2%) of 1151 of the recommendations were implemented; p = 0.357. The recommendation that was implemented least was 'Do not routinely order coagulation tests before invasive procedures', in which 28% stated that they applied this in clinical practice.

Conclusion. Four years after the introduction, only one-third of physicians and residents of internal medicine were aware of the Choosing Wisely Netherlands campaign. Nevertheless, most Choosing Wisely recommendations were implemented sufficiently in clinical practice. There is room for improvement, mainly in recommendations that need a multidisciplinary approach.

KEYWORDS

Choosing Wisely, quality improvement, unnecessary procedures

INTRODUCTION

To improve quality of care and reduce healthcare costs, reducing low-value care is a key element. Low-value care is care that is unlikely to benefit the patient given the cost, available alternatives, and preferences of patients.[1] In addition, this includes overuse of unnecessary medical care and this may cause harm to patients. Earlier research showed that approximately a quarter of all medical care is. unnecessary.[2] The Choosing Wisely campaign, a physician-driven campaign to create conversations between physicians and patients about unnecessary tests, treatments, and procedures, was launched by the American Board of Internal Medicine (ABIM) Foundation in 2012 to address low-value care.[3] At this moment, Choosing Wisely has spread to more than 20 countries worldwide. The 'Choosing Wisely Netherlands Campaign' started in 2014.[4] A main part of this campaign was the creation of Choosing Wisely recommendations by scientific societies, which are evidence-based lists of recommendations or 'Things Providers and Patients Should Question' to address commonly used low-value care.

The Netherlands Association of Internal Medicine (NIV) developed a list of recommendations of 10 wise choices. The development of the list was by a bottom-up approach, through a survey via e-mail to all NIV members asking for any item to be proposed. Three criteria for a Choosing Wisely recommendation were: (1) evidence based, (2) room for improvement in quality of care and/or costs, and (3) broad consensus. During an invitational conference all subspecialty societies discussed which 10 choices were

Table 1. *The 10 Choosing Wisely recommendations of internal medicine*

Number	Recommendation
1	Do not order laboratory tests more than twice a week in hospitalised patients unless clinically indicated
2	Do not place an indwelling urinary catheter in non-critically ill patient who can void
3	Do not order screening tests for clotting disorder in patients who develop first episode of deep vein thrombosis or pulmonary embolism
4	Switch from intravenous to oral antibiotics when possible, and consider discharge
5	Do not order plain abdominal or thoracic radiographs in patients with acute abdominal pain
6	Do not routinely order surveillance tests (PET or CT scans) in asymptomatic patients following curative-intent treatment of malignant lymphoma
7	Do not routinely prescribe medication for stress ulcer prophylaxis when start treating patients with corticosteroids
8	Do not routinely order coagulation tests before invasive procedures
9	Do prescribe medicines using generic names
10	Discuss whether treatment limitations are needed when talking to patients about treatment options

the best. This leaded to a list of 10 recommendations in Dutch (Supplementary Appendix)*. A translated version is found in table 1.

In the United States, early trends of seven Choosing Wisely recommendations showed only minimal benefits.[5] The next step in the Choosing Wisely campaign is a shift from recommendation development towards implementation,[6] because raising awareness of evidence about low-value care is generally insufficient to change clinical practice.[7,8]
In 2014, these Choosing Wisely recommendations of internal medicine were published and communicated explicitly by the NIV. In the present survey, we explored the current implementation of the Choosing Wisely recommendations of internal medicine. We aimed that minimal 80% of the physicians self-reported that the recommendation was implemented, then we presume the recommendation was part of regular care.

MATERIALS AND METHODS

We actively surveyed physicians and residents to determine the implementation of the Choosing Wisely recommendations in the departments of internal medicine in 2018. The survey was performed during a presentation about the Choosing Wisely Netherlands campaign by a PhD student of internal medicine (BJL). In addition to the survey, the goal of the presentations was to inform attendees once again about the campaign and the current status. For feasibility reasons, we visited half of all university medical centres (UMCs) in different parts of the Netherlands, and one teaching hospital and one nonteaching hospital in the direct environment of that UMC. The presentations were mostly planned during existing meetings, for example the morning report. During the presentation we asked all attendees to vote through VoxVote, which is a free mobile voting tool via the Internet. All attendees, physicians, and residents, were eligible to participate voluntary. The survey contained 11 closed-ended questions in Dutch, including the option 'not applicable'. Afterwards, there was a discussion per recommendation to evaluate possible barriers for the implementation. There was no incentive for completing the survey. The presentation can be found in the supplementary appendix.

STATISTICAL ANALYSIS

Categorical data were summarized as frequencies and percentages. Chi-square or Fisher's exact test were used to assess relationships between variables, especially the relationship between awareness of the Choosing Wisely campaign and total score of self-reported implementation of recommendations. A two-sided p value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and R software, version 3.6.1 (R Foundation, Vienna, Austria).

RESULTS

Between May 17th, 2018 and November 5th, 2018, we visited four UMCs, five teaching hospitals, and four nonteaching hospitals. We surveyed 281 physicians and residents of the departments of internal medicine, consisting of 158 respondents from a UMC, 91 from a teaching hospital, and 32 from a nonteaching hospital (table 2). We received 2625 answers via VoxVote, which is an 85% response rate of all starting participants. The results per hospital were send as feedback for internal use.

Four years after the introduction of the Choosing Wisely Netherlands Campaign, 178 (68.5%) of the 260 physicians were not aware of the international, national campaign, or the national Choosing Wisely recommendations of internal

Table 2. *Participating hospitals*

Hospital	City	Hospital Type	Date of presentation	Number of respondents
Amsterdam UMC, AMC	Amsterdam	UMC	May 17, 2018	46
Amsterdam UMC, VUmc	Amsterdam	UMC	August 10 and 21, 2018	44
Erasmus MC	Rotterdam	UMC	June 14, 2018	29
UMCG	Groningen	UMC	June 1, 2018	39
Dijklander Hospital, Hoorn	Hoorn	TH	August 22, 2018	18
Ikazia Hospital	Rotterdam	TH	July 10, 2018	25
MCL	Leeuwarden	TH	July 4, 2018	14
OLVG Oost	Amsterdam	TH	June 19, 2018	12
OLVG West	Amsterdam	TH	June 5, 2018	22
Admiraal De Ruyter Hospital	Goes	NH	November 5, 2018	7
BovenIJ Hospital	Amsterdam	NH	June 28, 2018	7
Dijklander Hospital, Purmerend	Purmerend	NH	September 26, 2018	11
MC Zuiderzee	Lelystad	NH	November 1, 2018	7

NH = nonteaching hospital; TH = teaching hospital; UMC = university medical centre.

Table 3. *Survey results about implementation of Choosing Wisely campaign and recommendations*

Question	Yes n (%)	No n (%)	NA n (%)	Total
Are you aware of the CW (Netherlands) campaign and/or the CW recommendations?	82 (31.5%)	178 (68.5%)		260
Do you apply the following CW recommendation during regular care?				
(1) Do not order laboratory tests more than twice a week in hospitalised patients unless clinically indicated	142 (57.0%)	75 (30.1%)	32 (12.9%)	249
(2) Do not place an indwelling urinary catheter in non-critically ill patient who can void	194 (78.5%)	16 (6.5%)	37 (15.0%)	247
(3) Do not order screening tests for clotting disorder in patients who develop first episode of deep vein thrombosis or pulmonary embolism	191 (78.6%)	21 (8.6%)	31 (12.8%)	243
(4) Switch from intravenous to oral antibiotics when possible, and consider discharge	212 (88.7%)	18 (7.5%)	9 (3.8%)	239
(5) Do not order plain abdominal or thoracic radiographs in patients with acute abdominal pain	184 (78.0%)	37 (15.7%)	15 (6.4%)	236
(6) Do not routinely order surveillance tests in asymptomatic patients following curative-intent treatment of malignant lymphoma	60 (25.9%)	27 (11.6%)	145 (62.5%)	232
(7) Do not routinely prescribe medication for stress ulcer prophylaxis when start treating patients with corticosteroids	157 (67.7%)	52 (22.4%)	23 (9.9%)	232
(8) Do not routinely order coagulation tests before invasive procedures	52 (22.9%)	135 (59.5%)	40 (17.6%)	227
(9) Do prescribe medicines using generic names	185 (79.1%)	35 (15.0%)	14 (6.0%)	234
(10) Discuss whether treatment limitations are needed when talking to patients about treatment options	129 (57.1%)	81 (35.8%)	16 (7.1%)	226

Data are n (%). CW = Choosing Wisely; NA = not applicable

Table 4. *Survey results without option 'not applicable'*

Applied CW recommendation	Yes n (%)	No n (%)	Total
(1) Do not order laboratory tests more than twice a week in hospitalised patients unless clinically indicated	142 (65.4%)	75 (34.6%)	217
(2) Do not place an indwelling urinary catheter in non-critically ill patient who can void	**194 (92.4%)**	16 (7.6%)	210
(3) Do not order screening tests for clotting disorder in patients who develop first episode of deep vein thrombosis or pulmonary embolism	**191 (90.1%)**	21 (9.9%)	212
(4) Switch from intravenous to oral antibiotics when possible, and consider discharge	**212 (92.2%)**	18 (7.8%)	230
(5) Do not order plain abdominal or thoracic radiographs in patients with acute abdominal pain	**184 (83.3%)**	37 (16.7%)	221
(6) Do not routinely order surveillance tests in asymptomatic patients following curative-intent treatment of malignant lymphoma	60 (69.0%)	27 (31.0%)	87
(7) Do not routinely prescribe medication for stress ulcer prophylaxis when start treating patients with corticosteroids	157 (75.1%)	52 (24.9%)	209
(8) Do not routinely order coagulation tests before invasive procedures	52 (27.8%)	135 (72.2%)	187
(9) Do prescribe medicines using generic names	**185 (84.1%)**	35 (15.9%)	220
(10) Discuss whether treatment limitations are needed when talking to patients about treatment options	129 (61.4%)	81 (38.6%)	210

Data are n (%). CW = Choosing Wisely.
Bold numbers indicate that these recommendations were implemented in clinical practice

medicine (table 3). In total, we had 2365 responses to the questions about the implementation of Choosing Wisely recommendations. We excluded the 362 'not applicable' answers; of all recommendations, 1506 (75.2%) of 2003 answers stated that they were applied in clinical practice. We found no differences in the reported implementation of the recommendations between responders who were aware versus those unaware of the Choosing Wisely campaign, 529 (76.1%) of 695 versus 854 (74.2%) of 1151; p = 0.357, respectively.

The percentages not applicable were less than 20% for all recommendations (table 3), except for recommendation 6 'Do not routinely order surveillance tests in asymptomatic patients following curative-intent treatment of malignant lymphoma'. For this, 62.5% of the attendees stated that this recommendation was not applicable to their clinical practice, because only haematologists treat these patients in the Netherlands.

The results without the option 'not applicable' are found in table 4. We found that half of the Choosing Wisely recommendations were sufficiently implemented, defined as minimal 80% of the physicians who self-reported that the recommendation was part of his or her regular care.

Table 5 shows the differences between hospital types. The awareness about the Choosing Wisely campaign was the lowest (22%) in the nonteaching hospitals in comparison with 37% in UMCs. Most results of the reported implementation of the Choosing Wisely recommendations were similar between hospital types. However, we found differences in four recommendations, indicating a better reported practice in nonteaching hospitals of recommendations 2 'Do not place an indwelling urinary catheter in non-critically ill patient who can void'; 6 'Do not routinely order surveillance tests in asymptomatic patients following curative-intent treatment of malignant lymphoma'; and 8 'Do not routinely order coagulation tests before invasive procedures'. Further, the implementation of recommendation 10 'Discuss whether treatment limitations are needed when talking to patients about treatment options' was better in teaching hospitals compared to the other hospitals.

DISCUSSION

Four years after the introduction of Choosing Wisely Netherlands campaign, only 32% of physicians and residents of the departments of internal medicine were aware of this campaign. In addition, this was even lower in nonteaching hospitals (25%). Nevertheless, half of the Choosing Wisely recommendations (numbers 2 to 5, and 9) are implemented in clinical practice. The other recommendations (1, 6 to 8, and 10) are not or insufficiently implemented in clinical practice.

Table 5. *Implementation of Choosing Wisely campaign and recommendations per hospital type*

Question	Hospital type	Yes n (%)	No n (%)	NA n (%)	Total
Know CW (Netherlands) campaign and/or CW recommendations?	UMC	45 (30.2%)	104 (69.8%)		149
	TH	31 (36.9%)	53 (63.1%)		84
	NH	6 (22.2%)	21 (77.8%)		27
Apply CW recommendation 1	UMC	79 (56.4%)	41 (29.3%)	20 (14.3%)	140
	TH	48 (58.5%)	23 (28.0%)	11 (13.4%)	82
	NH	15 (55.6%)	11 (40.7%)	1 (3.7%)	27
Apply CW recommendation 2	UMC	110 (79.1%)	6 (4.3%)	23 (16.5%)	139
	TH	58 (75.3%)	10 (13.0%)	9 (11.7%)	77
	NH	26 (83.9%)	0 (0.0%)	5 (16.1%)	31
Apply CW recommendation 3	UMC	108 (77.1%)	11 (7.9%)	21 (15.0%)	140
	TH	60 (80.0%)	8 (10.7%)	7 (9.3%)	75
	NH	23 (82.1%)	2 (7.1%)	3 (10.7%)	28
Apply CW recommendation 4	UMC	120 (90.9%)	9 (6.8%)	3 (2.3%)	132
	TH	63 (82.9%)	8 (10.5%)	5 (6.6%)	76
	NH	29 (93.5%)	1 (3.2%)	1 (3.2%)	31
Apply CW recommendation 5	UMC	101 (77.1%)	23 (17.6%)	7 (5.3%)	131
	TH	62 (80.5%)	11 (14.3%)	4 (5.2%)	77
	NH	21 (75.0%)	3 (10.7%)	4 (14.3%)	28
Apply CW recommendation 6	UMC	26 (19.7%)	17 (12.9%)	89 (67.4%)	132
	TH	21 (29.2%)	9 (12.5%)	42 (58.3%)	72
	NH	13 (46.4%)	1 (3.6%)	14 (50.0%)	28
Apply CW recommendation 7	UMC	89 (69.5%)	31 (24.2%)	8 (6.3%)	128
	TH	49 (66.2%)	15 (20.3%)	10 (13.5%)	74
	NH	19 (63.3%)	6 (20.0%)	5 (16.7%)	30
Apply CW recommendation 8	UMC	24 (19.5%)	78 (63.4%)	21 (17.1%)	123
	TH	15 (20.3%)	45 (60.8%)	14 (18.9%)	74
	NH	13 (43.3%)	12 (40.0%)	5 (16.7%)	30
Apply CW recommendation 9	UMC	97 (75.8%)	24 (18.8%)	7 (5.5%)	128
	TH	62 (82.7%)	8 (10.7%)	5 (6.7%)	75
	NH	26 (83.9%)	3 (9.7%)	2 (6.5%)	31
Apply CW recommendation 10	UMC	62 (49.6%)	53 (42.4%)	10 (8.0%)	125
	TH	55 (76.4%)	15 (20.8%)	2 (2.8%)	72
	NH	12 (41.4%)	13 (44.8%)	4 (13.8%)	29

CW = Choosing Wisely; NH = nonteaching hospital; TH = teaching hospital; UMC = university medical centre

The initial goal of Choosing Wisely was to raise awareness about overuse. However, this first step did not receive enough attention in the Netherlands. One explanation is that Choosing Wisely or the concept of overuse is not implemented in medical schools and residency programs, and thus does not reach medical students and residents. However, from 2016 to 2018, a project entitled 'Bewustzijnsproject' ('Awareness project') was implemented to increase awareness among residents for high-value cost-conscious care. Next, the

Choosing Wisely recommendations were published and communicated explicitly by the medical specialist societies without public and physician awareness campaigns, including for example, educational sessions, digital education materials, or social media attention.

The international spread of Choosing Wisely is promising and shows acceptance of the campaign. However, effectiveness has not been demonstrated in outcomes of quality and safety that are relevant to clinicians and patients.[6] A critical step is to raise awareness of unnecessary care and harm and waste, which results in a change of attitudes and behaviours from 'more is better' to 'more is NOT always better'.[4] However, after four years, only one-third of clinicians were aware of the Choosing Wisely campaign in the Netherlands. This seems similar to the United States, where approximately 20% of clinicians knew about the campaign after two years;[9] overall awareness among primary care physicians was higher four years after the start of the campaign at 40%.[10] Interestingly, in that survey, the authors found a relationship between awareness of the campaign and the report of fewer unnecessary tests or procedures in the past year. In contrast, we found no relation between awareness and the reported implementation of the recommendation.

Choosing Wisely recommendation 1 'Do not order laboratory tests more than twice a week in hospitalized patients unless clinically indicated' and 6 'Do not routinely order surveillance tests in asymptomatic patients following curative-intent treatment of malignant lymphoma' were followed by 65-70% of the respondents. This can be due to another national program, 'To Do or Not to Do?', which was introduced during the same time in the Netherlands to reduce unnecessary care.[11] From this program, two projects aimed to improve the same aspects as the Choosing Wisely recommendations 1 and 6. First, a multifaceted intervention reduced unnecessary laboratory tests by 11%,[12] amongst others, by a nationwide approach, during which, a toolkit in Dutch was developed to provide specific tools for healthcare workers focused on reducing unnecessary laboratory tests in hospitals.[13] A remarkable observation was that 60% of the internal medicine physicians and residents stated that recommendation 6 was not applicable for their clinical practices. One explanation is that the follow-up of patients treated for malignant lymphoma is explicitly performed by physicians in haematology departments. Since our results include all subspecialties in internal medicine, we do not know the implementation of this recommendation in the haematology departments. However, routine surveillance testing in asymptomatic patients leads to unnecessary radiation, possible false-positive outcomes, unnecessary anxiety, and psychosocial issues for patients, as well as accumulated costs.[14] Since CT scans are frequently routinely ordered and have a substantial false-positive rate, the improvement potential in quality of care and costs remain important.

More than 90% of respondents stated that they followed Choosing Wisely recommendation 2 'Do not place an indwelling urinary catheter in non-critically ill patient who can void'. However, this was a substantial problem in a recent quality improvement project in seven hospitals in the Netherlands, where inappropriate use of urinary catheters occurred in 32% of 324 patients.[15] For this project, the program 'To Do or Not to Do?' also developed a toolkit for further implementation in the Netherlands.[16]

The reported implementation of Choosing Wisely recommendation 4 'Switch from intravenous to oral antibiotics when possible and consider discharge' was very good. This could be due to the introduction of the antimicrobial stewardships (A) teams, which is successful probably due to obligation and surveillance by the Health and Youth Care Inspectorate (Inspectie Gezondheid en Jeugd) of the Netherlands. Furthermore, the is a growing awareness from the surgery departments for recommendation 5 'Do not order plain abdominal or thoracic radiographs in patients with acute abdominal pain'. Therefore, it is clear to healthcare workers that there is no added value of a plain abdominal X-ray.[17] Our results showed that there is also consensus in clinical practice regarding recommendation 3 'Do not order screening tests for clotting disorder in patients who develop first episode of deep vein thrombosis or pulmonary embolism', since screening tests for clotting disorders have no treatment implications.

We found a reasonable implementation of recommendation 7 'Do not routinely prescribe medication for stress ulcer prophylaxis when start treating patients with corticosteroids'. However, during discussion of the presentations, it appears that for this recommendation, the internal medicine physicians were dependent on the pharmacy. In several hospitals, respondents stated that the pharmacists regularly advised and offered proton-pump inhibitors (PPIs) to patients. Since low-dose PPIs are sold over-the-counter, patients do not need a prescription in the Netherlands. The actual implementation in clinical practice for patients is therefore unclear. In addition, recommendation 9 'Do prescribe medicines using generic names' is generally incorporated into the electronic prescription systems in the Netherlands. Since not all medicines have a generic name, a complete prescription in generic names is not possible.

The worst implemented recommendation was number 8 'Do not routinely order coagulation tests before invasive procedures'. In contrast to other recommendations, internal medicine physicians are dependent on radiologists for the implementation. In practice, a substantial part of the invasive procedures was performed by radiologists. However, they regularly demand a coagulation test (INR)

before procedures. Therefore, the implementation of recommendation 8 should be multidisciplinary, for example, in collaboration with the Radiological Society of the Netherlands (NVvR).

The final recommendation 10 'Discuss whether treatment limitations are needed when talking to patients about treatment options' was followed in 61% of respondents, mostly in teaching hospitals. In UMCs and nonteaching hospitals, only 50% followed this recommendation. During discussion of the presentation, most physicians declared that they consciously did not discuss possible treatment limitations in certain patient groups. For example, in the outpatient clinic, physicians did not discuss this with young patients without comorbidities and who had a short follow-up. Moreover, it is unclear, even among physicians, what the exact content of patient discussions should be, with respect to possible treatment limitations. If possible, the discussion should be held in an elective setting with the general practitioner, or with the treating physician in an outpatient setting.[18] In addition, the best way to discuss treatment limitations is unclear. It seems better to ask for any objections to certain procedures, for example, by asking "Are there any treatments or procedures that you do not want to receive?" instead of "I have one more routine question that I should ask. Do you wish to be resuscitated if your heart stops or you stop breathing?".[19]

The strength of this survey is the high response rate of 85% of the attendees to all questions and the multicentre design with an active assessment of the implementation of the Choosing Wisely campaign and recommendation in the Netherlands. The results should therefore be generalisable for all hospitals in the Netherlands, yet the results of this survey should be interpreted considering the limitations. The main limitation is that the results were based on self-assessment of internal medicine physicians and residents, because in general, healthcare workers overestimate themselves. Although they reported all answers anonymously, they could have reported more socially-acceptable answers. Another limitation is that the respondents only represented a part of our target populations, since we only included participants who were present during the survey day. Although our in-person survey was during a regular meeting (mostly after the morning handover), this could still introduce selection bias. Further, we could not distinguish physicians from residents, because participating in the active survey was completely anonymous and thus, did not collect any data about the respondents themselves.

CONCLUSION

In conclusion, after four years only one-third of internal medicine physicians and residents were aware of Choosing Wisely Netherlands campaign. Nevertheless, half of the Choosing Wisely recommendations were sufficiently implemented in clinical practice. There is room for improvement of the other recommendations, mainly in the recommendations that require a multidisciplinary approach.

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Conflict of interest statements

We declare no conflicts of interest.

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*Supplementary appendix is available from the authors upon request.

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ORIGINAL ARTICLE

Doppler follow-up after TIPS placement is not routinely indicated. A 16-years single centre experience

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ABSTRACT

Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective intervention to treat complications of portal hypertension. Since the introduction of polytetrafluoroethylene (PTFE)-covered stents, TIPS patency rates have improved, and the need for routine TIPS surveillance has become questionable. Aims of this study were to assess the indications, clinical outcome and survival, and yield of Doppler ultrasound follow-up in patients who received a TIPS in an academic centre.

Methods: A retrospective cohort study of all adult consecutive patients who underwent PTFE-covered TIPS placement between 2001 and 2016. Clinical, biochemical, and imaging findings were reviewed and analysed.

Results: A total of 103 patients were included for analysis. At one-year follow-up, control of bleeding was successful in 91% (41/45), and control of refractory ascites in 80% (8/10). In patients with variceal bleeding, a higher MELD score was a risk factor for 90-day mortality (HR 1.28 per point, $p < 0.001$) and one-year mortality (HR 1.24 per point, $p < 0.001$). In patients with refractory ascites, a higher MELD score was only a risk factor for 90-day mortality (HR 1.13 per point, $p = 0.03$). Doppler ultrasound investigations during follow-up revealed abnormalities in 4% (6/166), all of which were associated with clinical deterioration, while abnormalities were detected in 11.4% (19/166) of patients who presented with clinical symptoms of TIPS dysfunction.

Conclusion: The use of routine Doppler ultrasound follow-up after PTFE-covered TIPS placement seems unnecessary as it had a very low yield and abnormal Doppler findings were almost always associated with clinical symptoms of TIPS dysfunction.

KEYWORDS

Doppler, follow-up, meld, survival, TIPS

INTRODUCTION

Liver cirrhosis represents the late stage of chronic liver disease and is associated with portal hypertension (PH). Most frequent complications of portal hypertension are bleeding of oesophageal or gastric varices, (refractory) ascites, and hepatic encephalopathy (HE). Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is a highly effective intervention to reduce the portal pressure and to prevent rebleeding or treat refractory ascites.[1] Since the introduction of polyfluor-ethylene (PTFE)-covered stents, patency has increased and the rates of stent thrombosis and in-stent stenosis have decreased drastically.[2,3] Still, post-TIPS HE is a common (15-54%) complication that requires attention.[4,5] This complication can be treated in 95% of the cases with drug therapy.[6] However, patients often need hospital admission to undergo treatment.

There are few well-established prognostic markers that predict outcome after TIPS placement. The Model for End-stage Liver Disease (MELD) was initially developed to differentiate between patients who might benefit from TIPS and those who might not.[7] However, MELD does not predict post-TIPS complications like the development of HE. Furthermore, there is no consensus regarding follow-up after TIPS placement. Currently, TIPS patients stay under close surveillance in most centres to monitor patency of the shunt with Doppler ultrasound (US) with assessment of blood flow through the shunt. American Association for the Study of Liver Diseases (AASLD)

guidelines advise hospitals to have an established program for surveillance, but no specific intervals are suggested.[6] At our institution, patients undergo Doppler US at day 5-7 after TIPS placement, followed by Doppler US at 3, 6, and 12 months, and subsequently every 12 months. The hepatologist sees the patient one month after TIPS placement to start lowering diuretics, and after each Doppler US study. The aim of this study was to assess the indications, survival, clinical outcome and yield, and usefulness of Doppler ultrasound for predicting TIPS failure at 3, 6, and 12 months after PTFE-covered TIPS placement in a single-centre academic cohort. Specific markers were evaluated for early and long-term mortality in patients with TIPS placement for refractory ascites or variceal bleeding.

METHODS

Data of electronic health records of patients who underwent a TIPS placement in the Amsterdam University Medical Center, location Academic Medical Centre (AMC) between October 2001 and November 2016 were collected in a database. All patients with cirrhosis over the age of 18 years who received a PTFE-covered TIPS were included. Patients who received a TIPS for non-cirrhotic portal hypertension were excluded.

The following data were collected: age, gender, aetiology of cirrhosis, indication for TIPS, date and cause of death, baseline laboratory tests prior to TIPS placement, follow-up data regarding complications, development of HE, treatment outcome, details regarding TIPS placement (stent-size, dilatation, pressure measurements), reinterventions, and radiological follow-up data. MELD score was calculated with the following formula and associated assumptions: (0.957 * ln(serum creatinine in mg/dl) + 0.378 * ln(serum bilirubin in mg/dl) + 1.120 * ln(INR) + 0.643) * 10" (https://www.mdcalc.com/meld-score-original-pre-2016-model-end-stage-liver-disease). If only a prothrombin (PT) value was available, internationalised normal ratio (INR) value was derived from the PT value using corresponding normal limits.

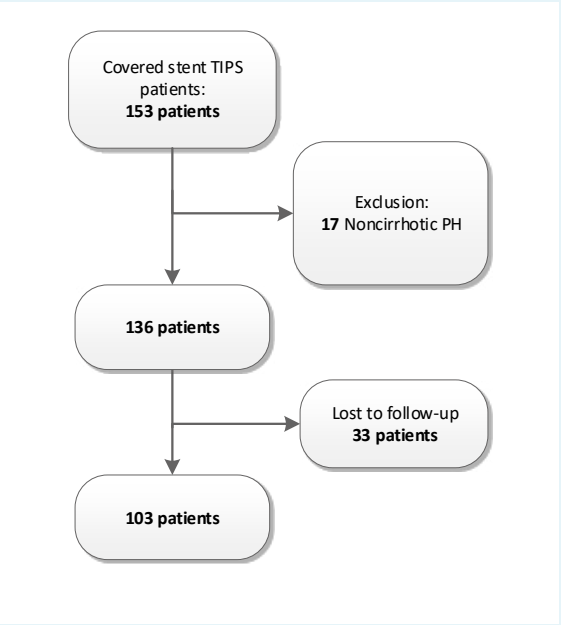
The electronic health record (EHR) was the primary data source. Missing clinical data were supplemented with data of paper patient files from the medical archive, data of referring hospitals EHRs, and information available at general practitioners. Missing radiological data were supplemented after reviewing the original images with an interventional radiologist (OvD).

Survival was defined as liver transplantation-free survival. Patients undergoing liver transplantation were censored at the day of transplantation. Patency of the TIPS was defined as last known Doppler US without signs of TIPS thrombosis or stenosis before liver transplantation, or previous re-interventions of a non-patent TIPS. To validate clinical improvement of ascites, this had to be either objectified by US or by physical examination, as documented in the EHR. New onset or deterioration of HE was interpreted from the EHR, using the West-Haven criteria. Rebleeding was defined as a documented variceal bleeding after TIPS placement. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the Medical Ethics Committee of the Academic Medical Centre in Amsterdam (reference number W17_093#17.112). For this type of study (retrospective) formal written consent was not required.

STATISTICS

Descriptive variables were expressed as mean (±SDs). Survival analyses were performed using Kaplan Meier curves, considering transplant-free survival. Log-rank test was used to compare cumulative survival among the groups. Independent t-test was used to compare numerical variables among groups, if normally distributed. Mann-Whitney U-test was used if numerical values were not normally distributed. Multivariate analysis was performed using Cox regression. All statistical analyses were performed with SPSS software (version 25.0; SPSS, Chicago, Illinois). Reported p-values are 2-tailed and considered statistically significant when the p-value was < 0.05.

Figure 1. *Flowchart of patients eligible for analysis*



PH = portal hypertension; TIPS = transjugular intrahepatic portosystemic shunt

Results

A total of 153 consecutive patients undergoing PTFE-covered TIPS placement were identified. Application of the exclusion criteria resulted in a total of 136 patients who were eligible for further exploration. Thirty-three patients were excluded from analysis since they were lost to follow-up. In total, 103 patients were included for analysis. A flowchart is provided in figure 1.

Baseline characteristics

Mean age at TIPS placement was 59 (± 12) years. Baseline characteristics are shown in table 1. Baseline characteristics for patients with variceal bleeding and refractory ascites are shown in table 2. Aetiology of liver cirrhosis was distributed equally between the two groups. Patients who presented with variceal bleeding were younger, had lower platelet counts, and lower serum albumin levels, while patients with refractory ascites had higher serum creatinine levels and lower sodium levels. There was no difference in MELD scores between these two patient groups.

Transplantation-free survival

Four patients underwent liver transplantation within 90 days after TIPS placement. Another three patients after this period. Ten patients (10%) died within the first 30 days. One patient suffered from acute congestive heart failure and in six patients, liver and/or renal function deteriorated (all these patients had a MELD score of 20 or above at TIPS placement). These high MELD scores were mainly based on high bilirubin levels, implicating impaired liver function. Two other patients died of sepsis and one of a cerebral haemorrhage. Within the first 90 days, a total of 25 patients had died (24%). The overall one-year transplant-free (TF) survival rate in this cohort was 56%.

Figure 2 shows the transplant-free survival of the patients with refractory ascites and variceal bleeding. Ninety-day survival rate was 84% in the variceal bleeding group and 62% in the refractory ascites group ($p = 0.04$). Survival rates after one year were 80% for patients with variceal bleeding and 27% for patients with refractory ascites ($p < 0.001$).

Cumulative survival at 90 days for patients with variceal bleeding and a MELD score < 20 was 97%, compared to 14% in patients with variceal bleeding and a MELD score ≥ 20 ($p < 0.001$; figure 3). Patients with refractory ascites had a 90-day survival of 66% when MELD score < 20, compared to 40% with MELD score ≥ 20 ($p = 0.12$).

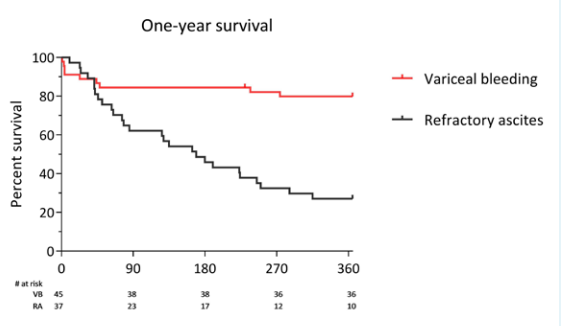
Kaplan-Meier survival curves, divided by Child-Pugh (CP) scores for variceal bleeding and refractory ascites are shown in figure 4. For patients with CP-B cirrhosis and variceal bleeding, one-year survival was 93% and 35% for CP-B patients with refractory ascites ($p < 0.001$). There was

Table 1. *Baseline characteristics – overall*

Population		
Mean age at TIPS (SD)	59	± 12
Male n (%)	72	(69.9)
Aetiology of cirrhosis n (%)		
Alcoholic	56	(54.4)
Cryptogenic	16	(15.5)
NASH	9	(8.7)
Cholestatic liver disease	7	(6.8)
Viral hepatitis	6	(5.8)
AIH	4	(3.9)
Viral hepatitis + alcohol	1	(1.0)
Alfa-1 antitrypsin deficiency	2	(1.9)
Other	2	(1.9)
Indication TIPS n (%)		
Variceal bleeding	45	(43.7)
Refractory ascites	37	(35.9)
Ectopic variceal bleeding	9	(8.9)
Preoperative	5	(4.9)
Hepatic hydrothorax	2	(1.9)
Other	5	(4.9)

AIH = autoimmune hepatitis; NASH = non-alcoholic steatohepatitis; SD = standard deviation; TIPS = transjugular intrahepatic portosystemic shunt

Figure 2. *Kaplan-Meier curve for 365-day survival, divided by indication for TIPS: variceal bleeding or refractory ascites. Comparing the variceal bleeding and refractory ascites group: 90-day survival was 84% compared to 62% ($p = 0.04$) and one-year survival: 80% compared to 27% ($p < 0.001$) using log rank test.*



RA = refractory ascites; VB = variceal bleeding

Table 2. *Baseline comparison of patients with refractory ascites and variceal bleeding. Values are shown as mean ± SD, or percentage*

	Refractory ascites (n = 37)	Variceal bleeding (n = 45)	p value
Age at TIPS	65 ± 8	54 ± 11	**< 0.001**
Male n (%)	26 (70.3)	33 (73.3)	0.76
Platelets (10e9/l)	159.9 ± 93.3	101.0 ± 55.8	**0.001**
Leukocytes (10e9/l)	7.2 ± 3.2	8.6 ± 5.8	0.11
INR	1.3 ± 0.3	1.4 ± 0.3	0.05
Prothrombin time (sec)	14.3 ± 3.8	16.0 ± 4.0	0.05
Sodium (mmol/l)	133.6 ± 5.7	137.9 ± 4.6	**< 0.001**
Albumin (g/l)	34.2 ± 5.4	29.9 ± 7.6	**0.004**
Creatinine (µmol/l)	120.4 ± 67.8	89.6 ± 58.9	**0.03**
Bilirubin (µmol/l)	32.3 ± 26.2	56.1 ± 97.1	0.79
Child-Pugh score n (%)			**< 0.001**
A	0 (0.0)	16 (35.6)	
B	26 (70.3)	15 (33.3)	
C	11 (29.7)	12 (26.7)	
MELD score n (%)			0.61
≤ 9	8 (21.6)	13 (28.9)	
10-19	24 (64.9)	22 (48.9)	
20-29	5 (13.5)	6 (13.2)	
30-39	0 (0.0)	1 (2.2)	

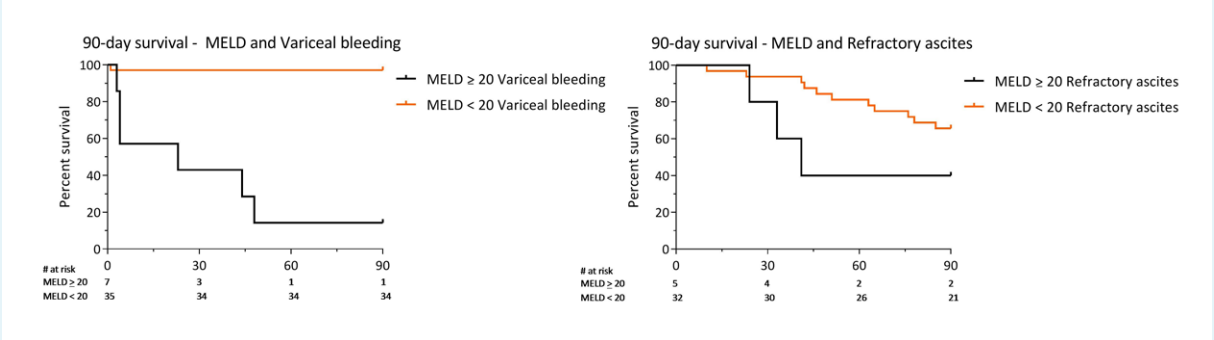
INR = international normalized ratio; MELD = Model for End-stage Liver Disease; TIPS = transjugular intrahepatic portosystemic shunt; SD = standard deviation

a trend for better one-year survival in patients with CP-C liver cirrhosis in patients with variceal bleeding (50%) compared to 9% in patients with refractory ascites.

Risk factors for mortality

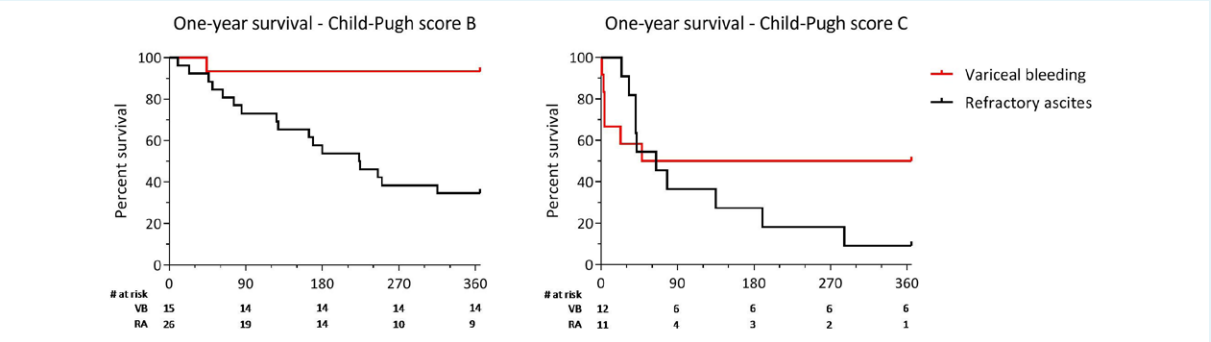
Risk factors for 90-day and one-year mortality, identified by Cox regression analysis, are shown in table 3. Factors were divided by the indications variceal bleeding and refractory

Figure 3. *Kaplan-Meier survival curves for 90-day survival, divided by MELD score < 20 and ≥ 20, for variceal bleeding (p < 0.001) and refractory ascites (p = 0.12) using log rank test.*



MELD = Model for End-stage Liver Disease

Figure 4. *Kaplan-Meier survival curves for one-year survival for Child-Pugh B and C patients, respectively. Survival for CP-B patients was 93% for variceal bleeding and 35% for refractory ascites (p < 0.001). CP-C patients had a one-year survival of 50% for variceal bleeding compared to 9% for refractory ascites (p = 0.27).*



CP = Child-Pugh; RA = refractory ascites; VB = variceal bleeding

ascites. For patients with variceal bleeding, as well as for patients with refractory ascites, a higher MELD score was a risk factor for 90-day mortality (HR 1.28 per MELD point increase, 95% CI: 1.14-1.46, p < 0.001 for variceal bleeding, and HR 1.13 per MELD point increase, 95% CI: 1.01-1.28, p = 0.03 for refractory ascites), while age was not (HR 1.00, 95% CI: 0.92-1.09, p = 0.97 for variceal bleeding, and HR 0.96, 95% CI: 0.89-1.04, p = 0.28 for refractory ascites). For one-year mortality, MELD score was only a risk factor for patients with variceal bleeding (HR 1.24, 95% CI: 1.11-1.38, p < 0.001) and not for patients with refractory ascites (HR 1.03, 95% CI: 0.95-1.12 p = 0.45).

Outcome variceal bleeding

Rebleeding from oesophageal or gastric varices within 90 days occurred in 2 of 45 patients (4.4%), both CP-C and within the first two weeks. Overall rebleeding rate within 12 months was 8.9%: a success rate to control bleeding of 91%.

Outcome refractory ascites

Figure 5 shows the outcome for refractory ascites patients after TIPS placement. Within 90 days after TIPS placement, 14 patients died (38%). Of the remaining patients, 12 of 23 (48%) showed clinical improvement of ascites, while the other half did not improve clinically in this first follow-up period. After six months, 22 patients (49%) had died. A total of 12 patients clinically improved and 6 patients had no clinical improvement of ascites. After 12 months, 27 patients had died (73%). Of the remaining patients alive (n = 10), 80% had benefit of TIPS placement. Two patients did not show clinical improvement after 12 months.

Development of HE after TIPS

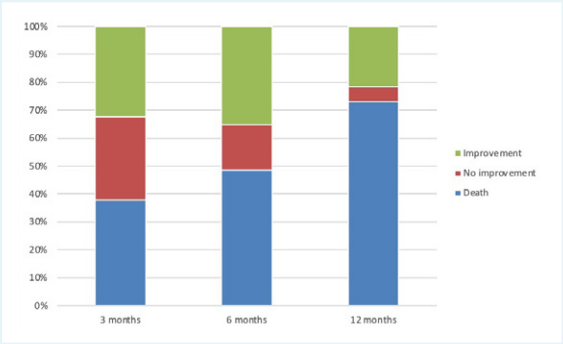
Clinically manifest HE within 30 days was reported for 37 patients (36%). Closure of the TIPS was necessary in two patients to resolve HE; all others could be treated with either lactulose or lactulose in combination with rifaximin.

Table 3. *Predictors of mortality*

Cox regression analysis						
3 A: 90-day mortality	**Refractory ascites**	**95% CI**	**p value**	**Variceal bleeding**	**95% CI**	**p value**
Age	HR 0.96	0.89-1.04	0.28	HR 1.00	0.92-1.09	0.97
MELD score	HR 1.13	1.01-1.28	0.03	HR 1.28	1.14-1.46	< 0.001
3 B: One-year mortality	**Refractory ascites**	**95% CI**	**p value**	**Variceal bleeding**	**95% CI**	**p value**
Age	HR 1.01	0.96-1.06	0.70	HR 1.00	0.93-1.06	0.89
MELD score	HR 1.03	0.95-1.12	0.45	HR 1.24	1.11-1.38	< 0.001

CI = confidence interval; HR = hazard ratio; MELD = Model for End-stage Liver Disease

Figure 5. *Outcome of refractory ascites. The left bar illustrates outcome at three months, the middle bar at six months, the right bar at twelve months.*



Three patients (2%) developed a coma hepaticum, of whom two died and one recovered with administration of oral and rectal lactulose.

TIPS patency and re-interventions

After 90 days, re-intervention free survival was 86%. Cumulative percentages of re-intervention free survival declined to 80% after two years (Mean time to re-intervention: 88 days (+ 74), range 6-230 days, median 71 days) A total of 166 Doppler US examinations were included for further analysis. Six TIPS revisions were performed after abnormalities were found during follow-up on Doppler US examination (3.6%) (thrombosis, stenosis, or flow change). All patients had clinical symptoms, most often increased ascites. Revisions were performed in 13 patients who had clinical symptoms and inconclusive Doppler US studies (7.8%). A total of 147 routine Doppler US procedures (88.6%) did not reveal any indications for re-intervention.

DISCUSSION

In this retrospective study, a markedly better one-year transplant-free survival was found in patients who had a TIPS placement for variceal bleeding (80%) in comparison to refractory ascites (27%) ($p < 0.001$). Survival was poor in patients with a MELD score ≥ 20, both in patients with variceal bleeding and refractory ascites. The number of reinterventions, after abnormalities on Doppler US were found, were low compared to the total number of performed surveillance Doppler US. Therefore, the need for ultrasound surveillance after TIPS placement can be questioned and probably does not add significant information to clinical evaluation.[8] We suggest that Doppler US can be left out of the follow-up in patients with ascites, since almost all patients had a clinical increase in ascites as a result of TIPS dysfunction. For patients with variceal bleeding this might still be a point of debate, since a rebleed could be associated with a higher mortality.[9]

Patients with CP-B and variceal bleeding had a better one-year survival (93%) compared to CP-B patients with refractory ascites (35%) ($p < 0.001$). On the other hand, in the first 30 days after TIPS placement, CP-C patients with variceal bleeding had a worse prognosis compared to patients with refractory ascites. This was probably due to the advanced disease state as variceal bleeding is a known life-threatening complication with high mortality in CP-C patients within the first days.[9]

After more than 30 days, prognosis was better for patients with variceal bleeding. After TIPS, the control rate of bleeding is high, and once bleeding is controlled in a patient, survival is relatively stable. Moreover, patients with refractory ascites often have more advanced liver disease, reflected by more patients with CP-B and CP-C cirrhosis in this group. Besides, patients with refractory ascites were also older in our cohort.

This study population showed an incidence of post-TIPS HE of 36%, which is in agreement with previously reported studies (15-54%).[4,5] However, this might be an underestimation due to the retrospective nature of this study and missing information to complete the West-Haven criteria. Treatment of post-TIPS HE is dependent on the severity and is patient specific. Mainly lactulose enemas were used in more severe cases whereas oral lactulose was the preferred first-line treatment in stage I-II HE. In two occasions, the TIPS had to be occluded to reduce complaints of HE. Post-TIPS HE is a severe complication, and unfortunately not easy to predict. Therefore, more studies in larger groups are needed to find markers that could select high-risk patients. Currently no prophylactic treatments are available to prevent post-TIPS HE. However, recently a multicentre, randomised, placebo-controlled, double blind study has started (NCT 04073290) to assess the prophylactic administration of rifaximin and lactulose to prevent post-TIPS HE.

The overall incidence of post-TIPS HE declined over time in our study cohort. One could suggest that this was the result of the introduction of rifaximin in the Netherlands in 2010. However, rifaximin is only prescribed to patients to prevent a third episode of clinical manifest HE while a history of clinical manifest HE is a contraindication for TIPS placement. We therefore presume that better and stricter selection of patients in combination with an increasing experience within our hospital with the use of TIPS in patients seems to be a more plausible explanation for the decline of HE over time.

Approximately 50% of patients with refractory ascites who survived 90 days after TIPS placement reported clinical improvement. This increased to 68% after 6 months,

and 80% after 12 months. Although one-year survival of patients with refractory ascites was only 27%, response rates were aligned with current literature (35-85%).[6,10] Therefore, in selected patients with refractory ascites, TIPS could be valuable. Standard post-TIPS diuretics dosage was 50% of the pre-TIPS dosage; further reduction was based on the clinical signs of the patient.

Control of variceal bleeding within the first year in our population was reached in 91% of the patients. This is similar to percentages mentioned in literature.[6] Early rebleed occurred in 4% of the patients and was lower compared to the 12.4% reported earlier.[6] However, uncovered stents were used in this previous study whereas only PTFE-covered stents were used in our cohort. It is unlikely that rebleeds were missed due to presentation elsewhere, because rebleeds are highly correlated with TIPS patency, which was reported back to our hospital.

TIPS patency was examined in a standardised manor with Doppler US. Flow velocities were compared to previous known velocities and flow direction was assessed. Patients who were evaluated for possible TIPS dysfunction all suffered from increased amount of ascites and clinical deterioration. Therefore, we suggest that routine follow-up should be implemented differently in the future. Follow-up by Doppler US can be omitted in patients with refractory ascites, if those patients do not suffer from (increased) complaints after TIPS placement. Patients, in whom the indication for TIPS was variceal bleeding, can be monitored less strictly than the current protocol, since TIPS patency rates are very high. Patients with cirrhosis are screened every six months for hepatocellular carcinoma at the outpatient clinic, and TIPS flow can be measured during this surveillance US if necessary. Our data support previous recommendations that regular surveillance is not necessary in the era of PTFE-covered stents.[11-14] A Doppler US examination might well be used to validate initial patency and to measure initial flow velocities. For further follow-up, Doppler US examination should only be done on indication.[8]

Our study has limitations. The retrospective nature of this study in combination with the relatively small number of patients in each group and missing data of incomplete patient records might have caused underreporting. Outcome values were reported as part of daily clinical practice and were not part of a study protocol, so could be biased by the reporting physician. Therefore, besides survival data, outcomes were not always exactly measured at the time points of 3, 6, and 12 months. The surprisingly high level of serum albumin in the refractory ascites group is difficult to explain and could be artificially high due to pre-procedural albumin suppletion.

In conclusion, overall transplant-free survival in our cohort was lower than previously reported mainly due to low one-year survival in patients with refractory ascites. Patients with variceal bleeding had an excellent overall one-year survival and very effective control of variceal bleeding. Routine Doppler US surveillance after PTFE-covered TIPS placement appears unnecessary as TIPS dysfunction was indicated by clinical deterioration rather than abnormalities found on routine Doppler US examinations.

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ORIGINAL ARTICLE

A healthcare failure mode and effect analysis to optimise the process of blood culture performance

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ABSTRACT

Background: Blood cultures are essential diagnostic tools to identify pathogens in systemic infections. However, logistics of blood culture performance is often suboptimal. This study analyses the pre-analytic phase of blood culture processing through different types of risk assessments.

Methods: We performed direct observations to gain in-depth knowledge of the root causes of suboptimal blood culture performance. These findings were summarised in a Bow-Tie chart. We then utilised a healthcare failure mode and effect analysis to prioritise failures per step in the process and to organise improvement activities. Finally, improvement actions were planned.

Results: Not obtaining a second set of blood cultures in the logistics of blood culture performance had the highest priority for action. Several failure modes, including human and system factors, were identified. Improvement actions included training and clinical lessons for nurses in the emergency department, updating hospital search engines to ease identification of relevant protocols, and an evaluation of the workload at the emergency department. Failure modes caused by human factors appear easy to address, however changing human behaviour is challenging.

Conclusions: The analysis provided useful insight into the different steps in the logistics of blood culture performance and facilitated the organisation of actions focused on addressing the most urgent root causes.

KEYWORDS

Blood culture, quality improvement, risk assessment

INTRODUCTION

Approximately 23% of all hospitalised patients in the Netherlands receive antibiotics due to a suspected bacterial infection.[1] Blood cultures are essential diagnostic tools to identify pathogens in systemic infections.[2-4] This identification is crucial for tailoring antibiotic treatment to pathogen-directed therapy, often resulting in a switch from intravenous to oral therapy. Both steps are essential for adequate antibiotic treatment, better patient outcomes, lower hospital costs, and, in the long run, a decrease in antimicrobial resistance.[5-8]

Based on previous studies, the current recommendations for adequate blood culture performance in most Dutch hospitals, including ours, requires collection of at least two sets of blood cultures from independent punctures with 8-10 ml blood per bottle prior to start of antibiotic treatment.[2,3,9-11] Previously, we have shown that blood culture results from two sets are available in only 48.8% of the patients who have an indication for blood cultures.[12] In our academic hospital, this percentage was even lower at 33%. This result, combined with a worldwide call for awareness on the appropriate use of antibiotics,[13,14] justified the initiation of a risk assessment into the root causes of suboptimal logistics of blood culture performance in 67% of our patients. The quality of a blood culture result relies largely on the quality of the pre-analytical phase and therefore we evaluated the whole process of blood culture performance starting from the ordering of blood cultures until the moment results are made available to the treating physician.

The quality system of our JCI-accredited hospital recommends proactive risk assessments as a method to improve systems of care.[15] Motivated staff members, including nurses, medical specialists, and quality

healthcare workers, are trained in two methods: the Bow-Tie method and the healthcare failure mode and effect analysis (HFMEA), to enable hospital-wide awareness and knowledge of risk assessment.

In the current study, we illustrated the utility of both methods in evaluating the process of blood culture performance.

METHODS

Hospital setting

Approximately 100 healthcare workers – both physicians and nurses – work in the emergency department (ED) and about 30,000 patients visit the ED every year.

Seventeen technicians work in the laboratory for medical microbiology. Nearly 12,500 blood culture sets are processed in the laboratory each year. On average, 77% of the blood culture samples are in the incubator within two hours of being drawn. No decentralised incubators are present in the hospital. Blood cultures are transported 24 hours per day, seven days per week by nurses, doctors, residents, and couriers. They place the blood cultures in the blood culture device. If a culture becomes positive, the blood is poured over an agar plate and incubated for approximately four hours. Thereafter, the colonies are tested by MALDI-TOF. in addition to this technique, we also prepare a Gram stain. When positive culture bottles are flagged, the initial result is reported to the clinic within two hours. The contamination rate of blood cultures was 3.2% of all sampled blood cultures, and 22.7% of the positive blood cultures in 2015.

Our laboratory is accredited according to the international standard (ISO) 15189 standards.

The Bow-Tie chart

To identify root causes of a suboptimal process of blood culture performance, we first gathered data through direct observations in the ED and the microbiology laboratory.

One researcher (MB) observed the process from the moment that a physician ordered blood cultures in the ED until the culture results appeared in the patient's electronic medical record. All acts and difficulties were reported using a standardised format, which included reporting of human errors, equipment problems, communication difficulties, or any other factor that disrupted the flow of blood culture processing. Additionally, the researcher asked healthcare workers involved in the process about their perception on possible risk factors for a suboptimal process of blood culture performance. Then we modelled our findings using a hospital Bow-Tie chart format. The Bow-Tie model combines the risk and protective factors of a so-called 'critical event' with its consequences in one figure.[16] Bow-Tie models have been used to evaluate risks in the petrochemical industry and aviation;[16-17] they have also been applied more recently to the medical field.[18,19] The 'critical event' refers to the final result that should be prevented, such as 'gas leakage'.[17] Therefore, we defined the 'critical event' as 'a suboptimal blood culture result' meaning that the pathogen is not identified.

The healthcare failure mode and effect analysis (HFMEA)

HFMEA originates from the failure mode and effect analysis that has been used successfully by other industries, including aviation.[20] The methodology of the HFMEA has been comprehensively described,[21,22] and it has also been applied in daily practice.[23-26] Briefly, a HFMEA involves the close examination of an error-prone process by a multidisciplinary panel. In this analysis, the process is divided into small steps. Potential failure modes and their consequences are identified per step. Although each potential failure mode has some effect on the efficiency of the process, each failure mode cannot be addressed at once. Priority is given to failure modes in which improvements are needed most. Therefore, risk scores are assigned to all identified potential failure modes. This risk score is based on likelihood of occurrence, severity, and detection. A high-risk score indicates priority for action.[20,21]

The information gathered in the Bow-Tie model was used as input for HFMEA. As with the Bow-Tie model, we used a chart that was designed by the quality and safety department of our hospital. Again, we evaluated the process from the moment that the physician ordered blood cultures in the ED until the culture results appeared in the patient's electronic medical record.

HFMEA started by establishing a multidisciplinary panel of key stakeholders and experts. The panel performed three brainstorm sessions resulting in identification of improvement actions. In a first brainstorm session, panel members were asked to suggest potential failure modes and their consequences in the process of blood culture performance. In a second session, they estimated which failure modes in the HFMEA had a high-risk score and thus, a high priority for action. These risk scores were based on the panel members' experiences. Possible categories for actions per failure mode were 'acceptation', 'control', 'elimination', or 'study' (in case more information was needed on the risk score of this failure mode). The multidisciplinary panel was also asked to identify potential risk-reducing interventions for the most urgent failure modes. In a third session, accomplishable interventions were planned. The facilitator updated the HFMEA chart after each session.

Institutional Review Board Approval

Since the study involved a quality improvement project at the hospital level with negligible risk of harming patients,

individual informed consent was waived. The Board of Directors of our institution approved the study.

RESULTS

The observations and short interviews were held in January 2015. Figure 1 presents our findings in the Bow-Tie chart. HFMEA was performed between January and September 2016. The panel consisted of one infectious diseases specialist, one acute care specialist, one medical microbiologist, two emergency department nurses, one quality officer, and one 'lean coach' from the microbiology department, who is specialised in the continuous optimalisation of working processes, with a focus on value and quality, and elimination of misconceptions. The facilitator was a researcher in the field of infectious diseases. Both the infectious disease specialist and the facilitator were trained in the Bow-Tie method and HFMEA by the Department of Quality and Safety. Table 1 presents the final chart.

The multidisciplinary panel determined that the lack of a second set of blood cultures was the problem with the highest priority for action. The absence of a second set of blood cultures was the consequence of several potential failure modes, including three human factors ('only one set ordered', 'misunderstanding that one set consists of two bottles', and 'forgot to take the second set'), one system error ('system provides stickers for only one set'), and one potential logistic factor ('no time to take the second set') (table 1). To address the human factors, we gave clinical lessons to nurses in the ED in July 2016. In these clinical lessons, we reminded nurses that blood culture sets consist of two bottles and that two sets are four bottles. Furthermore, we stressed the importance of a second culture set for the interpretation of the result (contamination or pathogen) and for increasing the chance of detecting the pathogen. In total, five lessons were given and approximately 90% of all nurses working in the ED joined at least one lesson.

We reasoned that use of the blood culture protocol could also guide appropriate blood culture sampling. Although our hospital did have a protocol for blood culture performance, it was not easy to find. Therefore, we updated the search engine of the protocol database in such way that, when searching for "blood cultures", "blood culture," or "blood culture performance" the correct protocol appeared directly. Search terms for the protocol were updated in June 2016. We promoted use of the protocol during the clinical lessons in July 2016. In October 2016, unit nursing officers sent an email to remind nurses to use the protocol.

To address the system error involved in obtaining a second blood culture ('system provides stickers for only one set'), we contacted the electronic medical system designers. They

Figure 1. *Bow-Tie model*

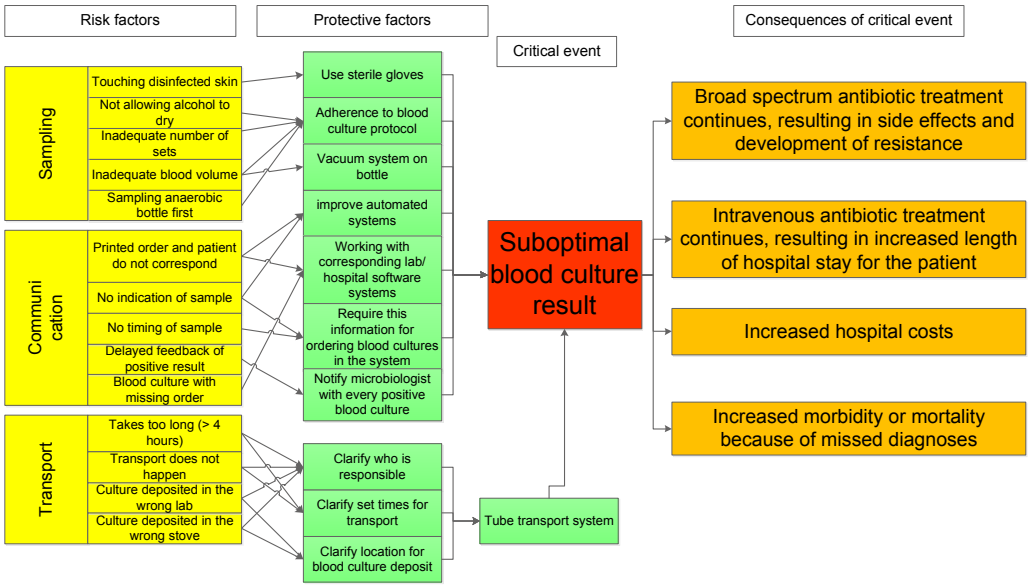


Table 1. *Health care failure mode and effect analysis workflow chart*

Step in process	Failure mode	Cause	Consequence	Frequency	Risk score	Action needed?	Action	Performed action
Order for two sets of blood cultures	Only one set is ordered	Human	Less chance of finding the pathogen, hinders interpretation of results	Daily	**High**	Yes, control	Education, promotion blood culture protocol	Clinical lessons, update protocol
	System provides stickers for only one set	System	Only one set is performed: Less chance of finding the pathogen, hinders interpretation of results	Daily	**High**	Yes, eliminate	Adapt the system	Involvement of designers of electronic medical system
	Misunderstanding that one set consists of two bottles	Human	Less chance of finding the pathogen, hinders interpretation of results	Daily	**High**	Yes, control	Education, promotion blood culture protocol	Clinical lessons, update protocol
Prepare sampling blood cultures	No proper disinfection	Human	Disturbance of culture result	Daily	**Medium**	Yes, control	Education, promotion blood culture protocol	Clinical lessons, update protocol
Sampling blood cultures	Too little blood volume	Human	Less chance of finding the pathogen	Daily	**Medium**	Yes, control	Education, promotion blood culture protocol	Clinical lessons, update protocol
	Too much blood volume	Equipment	Less chance of finding the pathogen	Not clear	**Low**	No, accept		
	Forgot to take the second set	Human	Less chance of finding the pathogen, hinders interpretation of results	Daily	**High**	Yes, control	Education, promotion blood culture protocol	Clinical lessons, update protocol
	No time to take second set	Logistics	Less chance of finding the pathogen, hinders interpretation of results	Not clear	**Unknown**	Yes, study	Test how often per shift a second blood culture has to be performed, and how important this risk factor is	Tested: conclusion is that the risk score is low
Cultures are placed in boxes for transport	Cultures placed in wrong place	Human	No or delayed blood culture result	Monthly	**Low**	No, accept		
Boxes are transported to the lab	No fixed time for transport	Logistics	Delayed blood culture result	Weekly	**Medium**	Yes, control	Hospital-wide system of couriers for cultures	Contact with logistic department: this system will be introduced in 2017
	Not clear who is responsible for transport	Logistics	Delayed blood culture result	Weekly	**Medium**	Yes, control	Hospital-wide system of couriers for cultures	Contact with logistic department: this system will be introduced in 2017
Cultures are placed in the incubator in the lab	Cultures are placed in the wrong lab	Human/ Logistics	Delayed or no culture result	Monthly	**Low**	No, accept		
	Cultures are placed in the wrong incubator	Human	Disturbance of culture result	Monthly	**Medium**	Yes, control	Hospital-wide system of couriers for cultures	Contact with logistic department: this system will be introduced in 2017
Cultures become positive	Not noticed by the technician (in the evening or weekend)	Logistics	Delayed feedback of blood culture result	Monthly	**Low**	No, accept		
Culture result is reported in the medical system	Forgot to place the result in the medical system	Human	Delayed feedback of blood culture result	Yearly	**Low**	No, accept		

developed a module in the electronic medical system in which the healthcare worker can choose to order one, two, or three sets of blood cultures and the number of required stickers are printed automatically. This module was finished in March 2018. In April 2020, a post-intervention sample analysis showed that two sets of blood cultures were performed in 85% of the patients.

Table 2. *Effect of extra personnel in the ED on the performance of two sets of blood cultures and culture results*

	Baseline measurement *June 15th – July 15th, 2016* **N (%)**	**Intervention measurement** *August 15th – September 15th, 2016* **N (%)**
Patients in whom blood cultures are performed in the ED	188 (100)	202 (100)
Patients with two sets of blood cultures	73 (39)	102 (50)
Patients with a positive blood culture result	34 (18)	34 (12)
Patient with contaminated blood culture result	11 (6)	10 (5)

ED = emergency department; N = number

Table 3. *Identified explanations for non-performance of the second blood culture set in the intervention period (August 15th – September 15th, 2016)*

	N (%)
Total number of patients in the ED in whom only one set of blood cultures was performed	100 (100)
Puncture did not succeed	4 (4)
Patient directly admitted to the ward after performance of the first blood culture set	2 (2)
Patient refuses another puncture	1 (1)
Nurse had performed the first set while blood culture performance was not indicated	1 (1)
Patient presented to the ED during the night (when the student was absent)	20 (20)
Patients without a second set of blood cultures without explanation	72 (72)

ED = emergency department; N = number

The panel members disagreed on which risk score needed to be assigned to the logistic failure mode 'no time to take the second set'. Therefore, the action 'study' was chosen to identify the urgency of this failure mode and to determine the effect of extra personnel on the number of blood cultures obtained per patient. Medical students were posted in the ED, seven days a week, 16 hours a day (between 7:00 AM and 11:00 PM), between the August 15th and September 15th, 2016. These students obtained the second blood culture set after the nurse sampled the first set. All students were trained in blood culture sampling. Nurses notified the students when an eligible patient was present and the students kept an eye on the registration board in the ED to make sure as few as possible eligible patients were missed. All nurses were informed about this test project in the clinical lessons by email and in a monthly newsletter. The number of blood cultures obtained per shift was determined using data that was extracted from the electronic medical system. The students reported observed explanations for not taking the second set of blood cultures on standardised forms. We extracted the number of patients admitted while the students were absent (between 11:00 PM and 7:00 AM) from the electronic medical system.

During this intervention period, 202 patients presented to the ED who required blood cultures, with an average of seven or eight patients per day, two or three patients per shift. Since several nurses work during one shift, a maximum of one patient per shift and per nurse needed blood cultures. Table 2 shows that the number of patients in whom two sets of blood cultures were taken increased by 11% in the intervention period (from August 15th until September 15th, 2016) compared to a baseline period (from June 15th until July 15th, 2016). Table 3 presents the explanations for not taking the second set during the intervention period. In the majority of the patients, no explanation was found.

We also started improvement actions on failure modes with an estimated medium risk score. 'No proper disinfection' and 'too little blood volume' during sampling were discussed using clinical lessons. To improve the transport of blood cultures from the emergency room to the microbiology laboratory, we approached the logistic distribution centre of our hospital. We enquired whether it was possible to hire a courier for the transport of cultures from the ED to the microbiology laboratory at fixed times. Personnel in the logistic distribution centre informed us that a hospital-wide distribution system would be implemented in 2020. Therefore, we optimised the current system (transport by ED assistants) for the remaining period, by scheduling one person who was responsible for the transport every two hours.

DISCUSSION

Method of risk assessment

The Bow-Tie model enabled us to gain in-depth knowledge of the root causes of a suboptimal process of blood culture performance. An important limitation of the Bow-Tie chart is that it does not allow identification of which risk factors are the most urgent. The Bow-Tie chart also did not allow prioritisation of interventions, which was an important limitation in determining which of the numerous departments involved in the process of blood culture performance should be targeted first. As a result, we struggled with translating the identified causes into actions to modify the process effectively for our purpose.

HFMEA provided useful insights in the different steps in the process of blood culture performance. The advantages of using a multidisciplinary panel are – amongst others – that it gives insight into the weaknesses of all steps of the process from different perspectives and that it provides mutual understanding. This approach helped to identify and prioritise failure modes of different steps in the process. These insights facilitated starting actions focused on the most urgent problems. The value of HFMEA in addition to the Bow-Tie model is demonstrated in identification of initial identified risk factors as described in in figure 1. Two risk factors in the Bow-Tie chart concern problems with the deposition of the cultures in the lab, while those were not classified as urgent in HFMEA. Also, some protective factors suggested in the Bow-Tie analysis – such as use of sterile gloves during blood collection – were not feasible in daily practice according to the multidisciplinary panel.

Furthermore, HFMEA demonstrated the importance of multidisciplinary communication. For example, without the involvement of the logistic distribution centre, we would currently be planning an improvement project for the transport from the ED to the microbiology laboratory concurrent to the upcoming hospital-wide distribution system.

Finally, HFMEA is usable in different situations. For example, while our analysis concerned an existing process, HFMEA has also been used to guide the implementation of a new technology.[25] A disadvantage of this broad utility is that it complicates direct comparison of HFMEA's performance due to the heterogeneity of processes.[23-26]

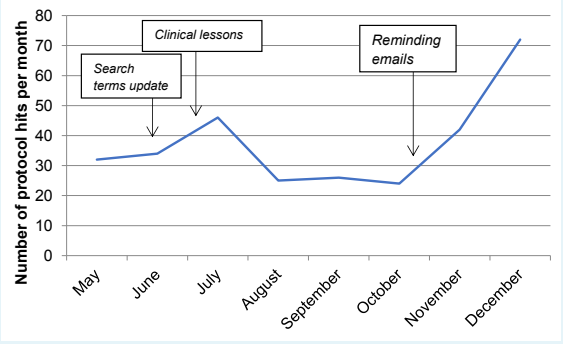
The most important disadvantage of performing HFMEA is that it can be very time consuming.[26] Failure modes can be identified using direct observations, surveys among physicians, or expert panels. Systematically, it would be preferable to use all three techniques. Logistically, however, it can be preferable to choose one technique. Since we executed direct observations for the Bow-Tie model and we performed a survey among physicians to identify barriers of – amongst others – blood culture performance earlier,[27] we only used the panel. During the panel meetings, we shared the knowledge from these earlier experiences. Also, we chose to estimate the risk scores based on expert opinion (the panel members). When consensus was lacking in the multidisciplinary panel - such as on the risk score of the failure mode 'no time to take the second set' – we collected data. This approach simplified the execution of HFMEA.

Blood culture process

The lack of a second set of blood cultures appeared to be the most important problem with the highest priority for action to improve the process of blood culture performance. Most failure modes were caused by human factors. Interventions focused on the human failure modes were relatively easy to accomplish. The effect differed per intervention, as illustrated by figure 2. Education and reminders should be incorporated into daily practice, since changing human behaviour is challenging and requires repetition.[28] An alternative intervention that could actually eliminate the problem of the lack of a second set is the introduction of the so-called 'single-sample strategy'. With this technique, the total volume of blood is collected from a single puncture, resulting in one 'blood culture set' existing of four to six bottles.[2,29,30] Although discrimination between contaminants and pathogens is no longer possible with this technique, it does guarantee the collection of an adequate volume of blood, which is the most important parameter for the detection of pathogens.[2,30]

It took nearly two years to address the systemic failure mode, but after implementation of the module in the electronic medical system, we saw an impressive increase in the performance of two sets of blood cultures, with two sets of blood cultures performed in 85% of the patients.

Figure 2. *Effect of interventions on blood culture protocol hits*



We studied how urgent the suggested logistic failure mode 'no time to take the second set' is. We saw that the number of patients, in whom two sets of blood cultures were taken, increased by only 11% in the intervention period compared to a baseline period, meaning that during the intervention period, 50% of patients still only had one set of blood cultures taken. In the majority of the patients without a second set of blood cultures, no explanation was found. These results showed that the failure mode 'no time to take the second set' does not have a high-risk score with priority for action. Taking two sets of blood cultures in one patient per shift should be feasible. Interestingly, increasing the personnel in the ED did not result in an enormous increase of two sets of blood cultures, suggesting that hiring more personnel is not the solution for the lack of a second set.

Although we have distinguished many steps in the process of blood culture performance, we did not include all details. For example, the quality of the materials used for blood culture sampling has not been evaluated.

The most important limitation of our risk assessment is that we did not measure the effect of the improvement actions separately. To be able to determine which intervention is the most effective, each improvement action should be tested separately and preferably compared to a control hospital without the improvement action. Nevertheless, it should be stressed that the aim of this risk assessment was to illustrate the effectiveness of the Bow-Tie model and HFMEA, to identify weaknesses in the process of blood culture performance and to optimise this process, not to develop an effective improvement action.

CONCLUSIONS

The Bow-Tie model helped to gain insight into the root causes of a suboptimal procedure, while the healthcare failure mode and effect analysis helped to identify the most urgent barriers in a process and to translate these findings into improvement actions. In the evaluation of the process of blood culture performance, the lack of a second set of blood cultures was identified as the problem with the highest priority for improvement. Several failure modes, including human and system factors, were identified. At first sight, failure modes caused by human factors seemed easy to address, however changing human behaviour appeared challenging. The implementation of a module in the electronic medical system to order two sets of blood cultures, resulted in the most improvement in the performance of two sets of blood cultures.

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DISCLOSURES

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ORIGINAL ARTICLE

Intraperitoneal treatment for advanced ovarian cancer, the Dutch experience. What did we learn?

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ABSTRACT

Background: Combined administration of intravenous (iv) and intraperitoneal (ip) (iv/ip) chemotherapy is an effective adjuvant treatment option after primary debulking surgery (PDS) for advanced ovarian cancer (OC). Increased toxicity and patient burden limit its use in daily practice.
Objective: To assess toxicity and survival outcomes of iv/ip chemotherapy in daily practice in the Netherlands.
Methods: This retrospective cohort study included 81 women who underwent at least an optimal PDS for FIGO stage III OC followed by iv/ip chemotherapy according to the Armstrong regimen, in four hospitals in the Netherlands between January 2007 and May 2016. We collected information on surgical procedure, abdominal port implantation, toxicity, and recurrence-free and overall survival.
Results: All participants underwent PDS, of whom 60 (74%) had their ip catheter implanted during PDS. Most frequently reported all grade toxicity was haematological n = 44 (54%). Forty-four patients (54%) completed all six cycles of iv/ip chemotherapy. The most frequent causes of discontinuation of iv/ip administration were renal dysfunction (12/37 = 32%) and catheter problems (7/37 = 19%). Median recurrence-free survival and overall survival were 24 months (range 0 – 108) and 80 months (range 4-115), respectively. Surgical outcome, completion of more than three courses of treatment and intra-abdominal localisation of recurrent disease were associated with better survival outcomes.
Conclusion: In daily practice, 54% of patients with advanced OC could complete all scheduled cycles of iv/ip chemotherapy with acceptable morbidity and toxicity, leading to outcomes comparable with the results of published trials on iv/ip chemotherapy.

KEYWORDS

Intraperitoneal, ovarian cancer, survival, toxicity, treatment

INTRODUCTION

In the Netherlands, 1,300 women are diagnosed with epithelial ovarian cancer (OC) annually.[1,2] Most patients are diagnosed with advanced, FIGO stage III disease. Standard therapy consists of either primary debulking surgery (PDS) followed by chemotherapy or neo-adjuvant chemotherapy followed by interval debulking surgery (IDS) and adjuvant chemotherapy. Cytoreductive surgery is centralised and performed in one of the eight Dutch gynaecologic oncology centres specialised in treatment of ovarian cancer. Intravenous (iv) chemotherapy consists of carboplatin and paclitaxel with or without bevacizumab. Median recurrence-free survival (RFS) in advanced

stage OC is 12 months and median overall survival (OS) is 24-50 months.[3-5]

Since 1996, several randomised studies have confirmed the superiority of intraperitoneal (ip) plus iv chemotherapy (iv/ip) over iv chemotherapy alone.[5-14] Armstrong et al. showed an improvement in median overall survival from 50 to 66 months for patients receiving iv/ip chemotherapy compared to iv chemotherapy.[5,15] This led to a clinical announcement by the United States National Cancer Institute in 2006 recommending iv/ip chemotherapy as treatment of choice for patients with OC with optimal (no residual mass larger than 1.0 cm in diameter) or complete (no visual residual mass) PDS.[5,10] Recently, another unpublished randomised trial using a lower dose of ip cisplatin combined with bevacizumab did not find a significant difference in RFS compared to iv carboplatin with weekly paclitaxel and bevacizumab.[16] Since OS data are not available and results have not yet been peer reviewed, it is unclear how this study should be valued. Nine randomised trials and three large meta-analyses on ip chemotherapy showed the superiority of ip chemotherapy over iv chemotherapy.[6,8,14,17] However, iv/ip administration of chemotherapy is still not common practice.[5,10] In the Netherlands, only a few centres treat patients with iv/ip chemotherapy after primary debulking surgery. In particular, the more severe toxicity cases, due to high dose of cisplatin (predominantly renal-, oto- and neurotoxicity), combined with paclitaxel (neurotoxicity), as well as abdominal pain and catheter complications are arguments against iv/ip chemotherapy.[5,10] Although iv/ip chemotherapy results in an impaired quality of life during treatment, quality of life recover after termination of iv/ip chemotherapy.[5,15]
Currently, the most effective evidence-based schedule for iv/ip chemotherapy is the schedule used by Armstrong et al.[5] Since 2007, four hospitals from three Dutch gynaecologic oncology centres offer this iv/ip chemotherapy schedule. The aim of this study is to evaluate both toxicity and survival outcomes of iv/ip chemotherapy in daily practice in the Netherlands.

METHODS

Setting and Participants

This observational study was performed in women diagnosed with FIGO stage III OC who had at least an optimal PDS (tumour rests 1 cm or less) and were treated with iv/ip chemotherapy in the Netherlands between January 2007 and May 2016 (n = 81). The in- and exclusion criteria were according to the Armstrong protocol.[5] In addition, the decision to give iv/ip chemotherapy was based on clinical condition and co-morbidity.

Procedures

All procedures (chemotherapy, dosage, reductions, discontinuation) have been performed according to the publication of Armstrong et al. (day 1 paclitaxel 135 mg/m2 in 24 hours iv; day 2: cisplatin 100 mg/m2 ip; and day 8: paclitaxel 60mg/m2 ip, to be repeated every 3 weeks for 6 courses).[5] Premedication and anti-emetics were given according to local standard treatment.[5]
For iv/ip therapy, a peritoneal catheter (9.6 Fr single lumen Bardport) was implanted either during PDS or afterwards by laparoscopic procedure. Ip catheters were removed after completion of treatment.
During consultation with the gynaecologic oncologists and medical oncologist, all eligible patients were informed on procedures of iv/ip chemotherapy, including survival benefit and treatment- related toxicity, after which, in a shared decision process, a choice was made for either iv or iv/ip adjuvant chemotherapy. After surgery, the patients received additional information from the medical oncologist and definitive informed consent was obtained.

Data collection

Retrospective data collection took place in May 2016. Patients have been prospectively registered between January 2007 and May 2016. The following clinical and patient information was obtained from the medical records: age at time of diagnosis, date of diagnosis, histological type of the tumour, surgical outcome after surgery, timing of implanting the abdominal catheter in relation to PDS, duration of follow-up (defined as time period between PDS and database lock), ip catheter-related morbidity (infection, obstruction, leakage), and chemotherapy related toxicity; nausea/vomiting, abdominal pain, haematological toxicity, electrolyte disturbance, impaired renal function, and neurotoxicity). RFS (defined as time period between PDS and first radiological proof of recurrence) and OS (defined as time period between PDS and death of any cause; this last variable was obtained from the Dutch Population Register). All toxicity was reported and graded according to common terminology criteria for adverse events (CTCAE) v4.0. In accordance with ethical standards, no ethical approval was needed.

Statistical analysis

Descriptive statistics of participants were performed for patient characteristics (table 1); course of iv/ip treatment and related morbidity and toxicity (table 2); and reasons for not completing six courses of chemotherapy (table 3). Cumulative survival analyses were performed from date of surgery with the Kaplan-Meier method (tables 4 and 5) and were compared with previously defined prognostic variables, surgical outcome (complete vs. optimal debulking), number of completed ip courses (1-3 vs. 4-6), age at diagnosis (≤ 60 vs. > 60 yrs), localisation of

Table 1. *Characteristics of the 81 patients with FIGO stage III ovarian carcinoma, treated with intraperitoneal chemotherapy*

	Total n = 81 (100%)
Age at diagnosis, years	
Median (range)	58 (29-77)
FIGO Stage n (%)	
III	81 (100)
IIIa	5 (6)
IIIb	4 (5)
IIIc	68 (84)
Unknown sub-staging	4 (5)
Residual disease after surgery[A] n (%)	
None	45 (56)
≤ 1 cm	33 (41)
Missing	3 (4)
Histology type[B] n (%)	
Serous	54 (67)
Mucinous	6 (7)
Endometroid	6 (7)
Clear cell	3 (4)
Carcinosarcoma	3 (4)
Adenocarcinoma NOS	4 (5)
Mixed serous/endometroid	2 (3)
Other or missing	3 (4)
Histology grade n (%)	
1	2 (3)
2	2 (3)
3	71 (88)
Missing	6 (7)
Catheter implantation n (%)	
During surgery	60 (74)
At laparoscopy	18 (22)
Missing	3 (4)
Presence enlarged of PALN before surgery n (%)	
Yes	16 (20)
No	54 (67)
Missing	11 (14)
Recurrent disease n (%)	
Yes	41 (49)
No	40 (50)
Localisation of recurrent disease n (%)	
Intra-abdominal	16 (40)
Extra-abdominal	18 (45)
Intra- and extra-abdominal	4 (10)
Missing	3 (8)
Death of disease n (%)	
Yes	25 (31)
No	55 (68)
Missing	1 (1)

[A] Complete = no residual mass, optimal = no residual mass greater than 1.0 cm
[B] NOS = not otherwise specified, other = unknown (n = 1) or undifferentiated (n = 2);
FIGO = International Federation of Gynecology and Obstetrics; n = number; PALN = para-aortic lymph nodes

recurrent disease (intra- vs. extra-peritoneally), presence of enlarged para-aortic lymph nodules (PALN) before surgery (yes vs. no), presence of dose reduction (no vs. yes), and start of chemotherapy (≤ 28 days vs. > 28 days).[5,10] Life expectancies were computed for the same groups by using the mortality rates to construct a life table (table 4). All statistical analyses were conducted using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Of the 89 OC patients who consented to iv/ip treatment, 81 were eligible for analysis. Eight patients were excluded from further analyses: 1 patient because of incomplete data, and 7 (8%) patients did not receive iv/ip chemotherapy. In the three cancer centres, 41, 27 and 13 patients (total n = 81) have been treated, respectively. Reasons not to start this treatment were: diagnosis of FIGO stage IV disease in 2 patients, pre-existent hearing loss in 2 patients precluding cisplatin treatment, post-operative perforation of gastrointestinal tract in 1 patient, post-operative infection in 1 patient, and progression of disease prior to start chemotherapy in 1 patient.

Patient characteristics are summarised in table 1. Median age at the time of diagnosis was 58 (range 29-77) years. All patients were diagnosed with FIGO stage III OC. All women underwent PDS; 45 (56%) had a complete PDS; 33 (41%) had an optimal PDS, of which, 3 (4%), patient information on residual disease after debulking surgery is lacking. The majority of patients were diagnosed with a high-grade serous carcinoma.

Abdominal catheter: implantation and complications

In 60 patients (74%,) the ip catheter was implanted during PDS, and 18 patients (22%) received the ip catheter during a laparoscopy, of which, patient information for 3 (4%) on catheter implantation is lacking. Seven patients (9%), had ip catheter complications, of whom, 3 (4%) continued iv/ip therapy after replacement of the catheter and 4 (5%) continued with iv therapy only.

Toxicity and morbidity

Toxicity and morbidity due to administration of iv/ip cisplatin and paclitaxel is summarised in table 2. Grade 3-4 toxicity was predominantly haematological (40%) or biochemical (21%). Although renal and neural toxicity was common, it was grade 3-4 in a minority of patients (both 4%). In 50 (62%) patients, no subjective toxicity was documented.

Median time between surgery and start of adjuvant treatment was 34 days (range 5-77 days). Forty-four patients (54%) completed all six cycles of chemotherapy. Forty-six

Table 2. *Course of intraperitoneal treatment and toxicity*

	Total n = 81 (100%)	
No of completed courses n (%)		
6 courses		
5 courses	44 (54)	
4 courses	8 (10)	
3 courses	5 (6)	
2 courses	3 (4)	
1 course	6 (7)	
	15 (19)	
Interval between surgery and start of chemotherapy		
Median (range)	34.5 (5-77)	
Dose reduction of Paclitaxel n (%)		
Yes	7 (9)	
No	68 (84)	
Missing	6 (7)	
Dose reduction of Cisplatin day 2 ip n (%)		
Yes	26 (32)	
No	49 (61)	
Missing	6 (7)	
Normalisation of CA125[A] n (%)		
Yes		
No	56 (69)	
Missing	15 (19)	
	10 (12)	
Toxicity	**Any grade n (%)**	**Grade 3-4 n (%)**
Nausea/vomiting	9 (11)	5 (6)
Abdominal pain	7 (9)	2 (2)
Haematological toxicity	44 (54)	32 (40)
Electrolyte disorders	35 (43)	17 (21)
Renal function disorders	32 (40)	3 (4)
Neurotoxicity	20 (25)	3 (4)

A Normalization of CA125 ≤ 35 E/mL
n = number

percent of the patients (37/81, table 2) discontinued the planned treatment. Reasons for discontinuation of iv/ip chemotherapy are summarised in table 3. Main reasons were impaired renal function, PAC dysfunction, or neurotoxicity. Dose reductions mainly occurred due to the toxicity of cisplatin.

Thirty-seven (46%) patients needed at least one dose reduction (7 patients needed a dose reduction of paclitaxel, 26 patients needed a dose reduction of cisplatin ip. For six patients, dose reductions were registered, not

Table 3. *Reasons for not completing six courses (n = 37), n (%)*

	Total n = 37 (100%)
Abdominal pain	2 (5)
Haematological toxicity	1 (3)
PAC problems[A]	7 (19)
Performance status	1 (22)
Electrolyte disturbances	3 (8)
Neurotoxicity	5 (14)
Renal function	12 (32)
Nausea vomiting	4 (11)
Progressive disease	1 (3)
Patient's request	1 (3)

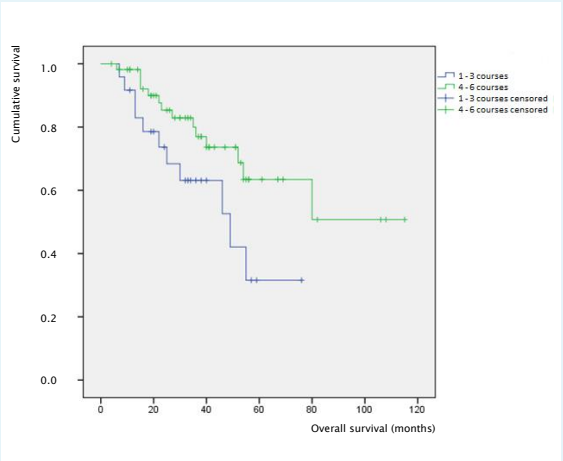
[A] PAC= abdominal implanted catheter, catheter related problems = decreased patency of the abdominal PAC.
n = number

specifying which drug. Of all 44 patients who completed the scheduled six cycles of chemotherapy, 19 (43%) needed a dose reduction, most frequently due to toxicity of cisplatin on the second day of treatment (4/16 = 25%, n = 3 missing).

Overall survival and recurrence-free survival

After completion of treatment, 56 (69%) patients had CA-125 normalisation. Median duration of follow-up was 40.0 months (range 4-115 months). One patient was lost to follow-up for survival analyses. During the follow-up

Figure 1. *Overall survival, moderated by number of completed ip courses (1-3 vs. 4-6)*



Cum = cumulative; OS = overall survival

Table 4. *One, two, and five-year overall survival and recurrence-free survival*

	OS (n = 80, 99%)	RFS	Complete debulking	Optimal debulking	Number of completed ip courses 1 – 3	4 – 6	Age at diagnosis ≤ 60 years	> 60 years	Localisation of recurrent disease intraperitoneally	Extraperitoneal	Intra- and extraperitoneal	Presence enlarged PALN before surgery Yes	No	Dose reduction Yes	No	Delay before start ≤28 days	> 28 days
OS, n	80	NA	42	32	**24**	**56**	50	28	**16**	**17**	**4**	15	54	46	34	25	48
1-year survival rate	96 (3)		95 (2)	97 (1)	**91 (2)**	**98 (1)**	96 (2)	96 (1)	**94 (1)**	**100**	**100**	100	96 (2)	100	91 (3)	96 (1)	100
% (n events)	82		79 (8)	83 (5)	**73 (6)**	**85 (7)**	84 (7)	78 (6)	**81 (2)**	**(0)**	**(0)**	(0)	80 (9)	(0)	81 (6)	87 (3)	(0)
2-year survival rate	(13)		72 (9)	33	**27**	**62**	60	33	**49 (7)**	**70 (5)**	**75 (1)**	93 (1)	44	82 (7)	68 (9)	51	82 (7)
% (n events)	52		0.051	(14)	**(11)**	**(13)**	(13)	(11)	**0.024**	**24**	**75 (1)**	82 (2)	(17)	33		(10)	60
5-year survival rate	(24)				**0.041**		0.337			**(10)**		0.121		(15)		0.819	(11)
% (n events)	NA													0.228			
p-value																	
RFS, n	NA	77	**43**	**31**	23	54	47	28	16	17	4	16	52	45	32	24	46
1-year survival rate		81	**80 (8)**	**83 (5)**	73 (6)	86 (7)	84 (7)	79 (6)	75 (4)	53 (8)	75 (1)	94 (1)	81 (9)	83 (7)	81 (6)	87 (3)	84 (7)
% (n events)		(14)	**60**	**38**	42	54	57	40	19	18	25 (3)	73 (4)	41	42	59	71 (6)	67
2-year survival rate		48	**(15)**	**(17)**	(12)	(21)	(17)	(16)	(13)	(14)	0 (4)	29 (7)	(25)	(21)	(12)	51 (8)	(12)
% (n events)		(34)	**45**	**13**	42	30	35	29	0 (16)	0 (17)		0.111	24	25	37	0.424	67
5-year survival rate		31	**(18)**	**(21)**	(12)	(28)	(22)	(18)	0.904				(29)	(23)	(17)		(12)
% (n events)		(40)	**0.045**		0.561		0.245							0.378			
p-value		NA															

Significant outcomes are presented in bold
n = number; N/A = not applicable; OS = overall survival; PALN = para-aortic lymph nodules; RFS = recurrence-free survival

period, 41 patients (49%) had recurrent disease and eventually, 25 (31%) patients died. The median RFS and OS were 24 (range 0-108) and 80 (range 4-115) months, respectively. Results of OS are listed in table 4. Those who completed 4 to 6 courses of iv/ip chemotherapy (p = 0.041, figure 1.) and those who had ip localisation of recurrent disease (p = 0.024) had significantly better OS than those who received 3 or fewer courses of iv/ip chemotherapy and those with extra-peritoneal recurrence of OC. All other characteristics were not significant. Those who underwent a complete debulking had significant improvement of RFS compared to those who had an optimal but not complete debulking (p = 0.045). There was no significant association between other factors and outcome variables.

DISCUSSION

In this study, we investigated the use of iv/ip chemotherapy for OC in the Netherlands between January 2007 and May 2016. Four hospitals from three gynaecological cancer centres prescribed ip/iv chemotherapy for a minority of their patients. With the strict selection criteria described by Amstrong et al., results in daily practice were more or less comparable with the study results concerning toxicity and RFS. The reasons for toxicity with iv/ip chemotherapy are two-fold: the dose of ip in the cavity is higher than can be administered iv, and the slow uptake of cisplatin from peritoneal surfaces, results in prolonged systemic exposure.[10]

Fifty-four percent of the patients diagnosed with FIGO stage III OC who received iv/ip treatment were able to complete six cycles according to the Armstrong regimen. This is not worse than the 42% in the original report of Armstrong et al.,[5,10] or the 12.7% reported by Wright et al. It is slightly lower than Schlappe et al., who reported 62% completion,[11,12] but they used a different regimen with a lower dose of cisplatin (75 mg/m^2) and administered carboplatin instead of cisplatin.[11] Due to the retrospective character of our study, toxicity data were not always complete. Abdominal pain as a cause for discontinuation of treatment occurred in 9% of the patients, which is similar to other studies.[11,18] Other adverse effects were similar to those previously reported.

Catheter complications occurred in 9% of the patients, while Schlappe et al and Walker et al. reported port problems in 9% and 34% of their patients, respectively.[11,18] We hypothesise that the better completion rate over time may be due to improved experience with placing and using ip catheters and the centralised care.[19] The selection of patients in order to increase completion rate (such as younger age and better performance status) may also have had a substantial role.

Dose reductions in our study were mostly used to decrease the toxicity of cisplatin. Recent studies by Mackay et al. and Hasegawa et al. with ip treatment using carboplatin, showed comparable data for survival and ip port-related toxicity, but less systemic toxicity.[20-23] Carboplatin instead of cisplatin in ip treatment for epithelial ovarian cancer may thus be a better alternative in terms of toxicity, but efficacy is unproven. Preclinical studies have shown that the tumour penetration of cisplatin is better than carboplatin, suggesting a pharmacokinetic advantage of cisplatin over carboplatin in achieving local high concentrations such as in ip administration.[24]

A recent study of Walker et al.[25] revealed no advantage to the use of the modified ip cisplatin regimen compared with the more conventional iv drug administration. It is noteworthy that in this study, cisplatin was administered in a dose of 75 mg/m^2 instead of 100 mg/m^2 and was also combined with bevacizumab. Moreover, recent studies revealed that addition of bevacizumab (VEGF-inhibitor) to the standard three weekly carboplatin paclitaxel has similar survival rates but with less toxicity (less sensory neuropathy).[25,26] New treatment strategies with, for example, maintenance parp inhibitors combined with other targeted agents may improve the prognosis of OC in the near future, hopefully leading to less (long-term) toxicity.

The presence of PALN during debulking surgery and information on catheter implantation are important prognostic and therapeutic criteria to select patients eligible for ip treatment. PALN might be a sanctuary side for the ip chemotherapy[27] and during second look catheter implantations, presence adhesions could be an indication of potential treatment failure.[28,29] It is to be expected that in the near future a personalised treatment plan, predicted by tumour and personal characteristics, will further improve the cure and care of these patients. The use of iv/ip treatment should then be reassessed.

Unfortunately, we did not record information on patient experience. The study of Walker et al. reported that patients who received ip treatment experienced significantly worse symptoms, especially abdominal discomfort.[18] IP treatment results in an impaired quality of life during treatment; however, this recovers after termination of therapy. It would have been interesting to evaluate this in daily practice.

As toxicity is the main drawback of iv/ip chemotherapy, research to mitigate this is important. Prior research showed that co-administration of epinephrine and cisplatin might lead to a decrease of toxicity. IP administration of epinephrine increases the penetration of platinum derivatives into tumours.[30] However this does not seem common practice in iv/ip chemotherapy. Another way to decrease toxicity might be the use of thiosulphate. Within minutes after administration of cisplatin, the highly toxic monoaqua hydrolysis complex (MHC) is formed.[31] Thiosulphate modulates the metabolism of cisplatin in plasma by rapidly reacting with the MHC to form platinum-sulfur complexes.[31] By using thiosulphate as a possible chemoprotective agent in animal studies, toxicity of cisplatin was reduced, often without appreciably affecting its anticancer efficiency.[31,32] Thiosulphate was also used in the recent published HIPEC trial of van Driel et al.[33,34] Prospective studies with epinephrine and thiosulphate in iv/ip are warranted in order to investigate possible decrease of toxicity of iv/ip treatment in OC.

HIPEC with cisplatin after primary debulking may be another strategy to improve outcome after primary debulking surgery in the light of the recently published positive results of HIPEC after interval debulking. A study protocol for this is under development.[20,21,35]

We did not find evidence of a difference in RFS and OS for older patients, although drug metabolism and renal function may be impaired in the elderly (even in the presence of creatinine levels within the normal range).[36] This seems to justify treatment with this regimen on the basis of functional status rather than age alone.

Many patients considered candidates for iv/ip chemotherapy (based on disease characteristics) in the Netherlands do not receive this treatment.

In order to estimate the potential population which could be candidate for iv/ip chemotherapy, we assessed the number of patients with FIGO stage III and optimal or complete debulking registered in the Netherlands Cancer Registry (NCR) in the comprehensive cancer centres of the hospitals providing iv/ip chemotherapy in the same period. After linking the eligibility criteria of our study to the NCR data, n = 1447 women with FIGO stage III disease were registered who had at least an optimal PDS, and were living close to the hospitals using iv/ip chemotherapy. Only 6% of the patients were actually treated with iv/ip therapy in the region of the hospitals offering iv/ip chemotherapy in the past eight years. Even allowing for insufficient functional status and/or patient preference, this number seems low. A lack of familiarity with ip administration procedures, perceived toxicity, or financial incentives leading to inadequate referral to ip/iv centres may be part of this gap between eligibility and actual treatment.[5,10,12] In the US, a recent report of Medicare beneficiaries found that

only 3.5% of women with OC received iv/ip chemotherapy.[12] Moreover, if we would reflect on all eight Dutch centres that treat OC, the percentage of Dutch patients receiving iv/ip chemotherapy would be even lower.

One way to improve patient referral for iv/ip chemotherapy is developing uniform patient information leaflets and shared decision-making tools which are available in the centres that apply iv/ip chemotherapy, should be available for all patients in the Netherlands. Currently, a project addressing this issue is in progress. In addition, optimal referral with discussion in expert multidisciplinary teams (leading to survival gain), before and after primary surgery, with optimisation of patient selection and patient counselling, education of referring physicians, and overcoming logistical hurdles, including financial incentives, will be key.[5,10-12,37-40] Further research after adjustment of therapy regimen and co-administered medication is also needed to decrease or palliate toxicity.

This study has several limitations. First, the sample size is small. Second, toxicity was not reported with the rigor of a randomised controlled trial. For this reason, some data on morbidity and toxicity are lacking and may have led to underreported results. Third, we lack detailed information about the performance status of patients during iv/ip treatment and were unable to correlate results with this factor. Despite these limitations, the current study contributes new findings based on nationwide, multicentre data. We succeeded in collecting data on all patients who have been treated with ip chemotherapy since 2006 until 2015, from all institutes in the Netherlands that apply this treatment modality.

CONCLUSION

Toxicity, RFS, and OS of ip chemotherapy administered in daily practice in the Netherlands, for patients with advanced, at least optimally debulked OC, leads to similar results as those reported by Amstrong et al. in a randomised controlled trial.

DISCLOSURE

The authors have declared no conflicts of interest.

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ABBREVIATIONS	
OC	ovarian cancer
PDS	primary debulking surgery
IDS	interval debulking surgery
iv	intravenous
ip	intraperitoneal
OS	overall survival
HIPEC	hyperthermic intraperitoneal chemotherapy
PIPAC	pressurised intraperitoneal aerosol chemotherapy
NCR	National cancer registry
CTC	common toxicity criteria
NOS	not otherwise specified
PALN	para-aortic lymph nodules
RFS	recurrence-free survival
MHC	monoaqua hydrolysis complex

ORIGINAL ARTICLE

Prediction admission in the older population in the Emergency Department: the CLEARED tool

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ABSTRACT

Background: Length of stay (LOS) in the Emergency Department (ED) is correlated with an extended in-hospital LOS and may even increase 30-day mortality. Older patients represent a growing population in the ED and they are especially at risk of adverse outcomes. Screening tools that adequately predict admission could help reduce waiting times in the ED and reduce time to treatment. We aimed to develop and validate a clinical prediction tool for admission, applicable to the aged patient population in the ED.

Methods: Data from 7,606 ED visits of patients aged 70 years and older between 2012 and 2014 were used to develop the CLEARED tool. Model performance was assessed with discrimination using logistic regression and calibration. The model was internally validated by bootstrap resampling in Erasmus Medical Center and externally validated at two other hospitals, Medisch Spectrum Twente (MST) and Leiden University Medical Centre (LUMC).

Results: CLEARED contains 10 predictors: body temperature, heart rate, diastolic blood pressure, systolic blood pressure, oxygen saturation, respiratory rate, referral status, the Manchester Triage System category, and the need for laboratory or radiology testing. The internally validated area under the curve (AUC) was 0.766 (95% CI [0.759;0.781]). External validation in MST showed an AUC of 0.797 and in LUMC, an AUC of 0.725.

Conclusions: The developed CLEARED tool reliably predicts admission in elderly patients visiting the ED. It is a promising prompt, although further research is needed to implement the tool and to investigate the benefits in terms of reduction of crowding and LOS in the ED.

KEYWORDS

Aging patient population, crowding, emergency department, prediction model, triage

INTRODUCTION

Elderly patients represent a growing population in the Emergency Department (ED).[1-3] Older patients, defined as aged 70 years and over, are overall more vulnerable than the general adult population. They have less physical endurance, are more likely to have multiple co-morbidities,[4] and are also more susceptible to polypharmacy and associated risks.[5] In the ED, elderly patients have a longer length of stay (LOS) compared to younger patients.[6-9] This can be partly explained by an atypical and non-specific presentation of illnesses in the ED.[10-12] Moreover, symptom-based triage classifications tend to underestimate the severity of disease,[13-15] whilst elderly patients visits in general have a greater level of urgency.[6,16] As a consequence, care for elderly is more complex and elderly patients are more often assessed by multiple specialists.[17] LOS in the ED is associated with poorer quality of care and may have negative effects on outcomes for the individual patient. Time spent in the ED

correlates strongly to the total LOS in the hospital,[18] and periods of longer LOS due to ED crowding are associated with increased inpatient mortality.[19] Predicting which patients should be admitted directly after presentation to the ED may reduce waiting times and time to treatment whilst improving diagnostic trajectories and quality of patient care. It has been suggested that new strategies to decrease ED LOS can decrease patient morbidity and healthcare expenditure.[20,21] Certain patient characteristics, such as aberrant vital parameters, have been shown to be predictive for admission,[22,23] yet it is unknown which set of predictors contributes most to admission.

We aimed to develop and validate a prediction model for admission, using non-invasive and readily available variables, applicable to the general elderly population at the ED.

MATERIALS AND METHODS

Study design

We performed a retrospective cohort study. Data from one hospital was used for model development and data from two other hospitals were used for external validation.

Setting and participants

For model development, data were acquired from a large consecutive ED cohort in the Erasmus University Medical Centre, Rotterdam (Erasmus MC), the Netherlands, including all patient visits in the ED from January 1st, 2012 until June 30th, 2014. This ED is a level 3 trauma centre and is situated in the largest hospital in the Netherlands, with 30,000 patient visits annually. Elderly patients, defined as people aged 70 years and over, were selected from this database. Both the first visit of a patient as well as repeat visits were included. Patients were excluded when they died on presentation or died during the ED visit.

For external validation, data from the Leiden University Medical Centre (LUMC), which is the academic hospital situated in Leiden, the Netherlands, with approximately 27,000 ED visits annually, and the Medisch Spectrum Twente (MST), a large teaching hospital in Enschede, the Netherlands, with approximately 26,500 ED visits annually, were used. In the LUMC, data were used from an existing database with patients visits in the ED in 2012. For external validation in MST, data were collected from all patients visiting the ED within the first three days of each month in 2015.

Variables and measurement

Outcome was defined as admission or transfer to another hospital for admission, and was collected from the patient records. Basic characteristics including information on sex and age were retrieved from the patient records. Additional ED arrival information was extracted from the patient charts, containing time of arrival and discharge from the ED, triage classification based on the Manchester Triage System,[24] vital parameters at arrival (blood pressure (in mmHg), heart rate (per minute), respiratory rate (RR) (per minute), body temperature (in degrees centigrade), peripheral oxygen saturation (SpO_2, in percentage), state of consciousness using the AVPU[25] or Glasgow Coma Scale scoring system[26] (AVPU/GCS), laboratory testing (yes/no), radiology testing (yes/no), and referral status to the ED (i.e., by ambulance, self-referral, by general practitioner).

After merging all the different variables from the patient record, the patients were coded in order to anonymise the collected data. Only contributors to the study had access to the database. This study was evaluated and approved by the Medical Research Ethics Committee of the Erasmus MC.

Potential predictors were categorised based on to their normal values. Body temperature was categorized in four groups (≤ 35.9, 36.0-37.0, 37.1-38.4, ≥ 38.5 °C). Heart rate was classified in three categories based on the categories used in the Modified Early Warning Score (MEWS). The MEWS is a guide to aid in recognition of deteriorating patients and is based on physiological parameters.[27] In order to facilitate a clear model, the original five MEWS categories were reduced to three (≤ 50, 51-100, > 100 bpm). Both systolic and diastolic blood pressure were coded according to the current definition of hypotension (< 90 vs. < 60 mmHg) and hypertension (> 140 vs. > 90 mmHg) for systolic and diastolic blood pressure, respectively. RR was categorised according to the definition of bradypnoea (< 12 times per minute), normopnoea (12-20 times per minute), and tachypnoea (> 20 times per minute). SpO_2 was classified in three groups (≤ 92, 93-97, ≥ 98%). Finally, referral status in the ED was coded in three classes based on whether patients were (1) referred by any specialist or general practitioner; (2) arrived by ambulance, in which case the ambulance nurse decided to present the patient at the ED; or (3) were self-referred. In every parameter a missing value category was created to make the model better applicable in daily practice.

Statistical methods

Univariate logistic regression was used to assess the association between potential predictors and admission. The predictive value was assessed and quantified with the Akaike Information Criterion (AIC) based on the Likelihood Ratio χ^2 ($LR\chi^2$). The AIC is a measure of the relative quality of a model or a parameter and can be used when the database is large and selection on p value will result in a large number of selected parameters.

The selected predictors from the univariate analysis were combined in a multivariate model and selection of the final set of predictors was based on added values of each predictor (based on the AIC) and clinical knowledge.

The performance of the model was calculated using the Area Under the Receiver Operating Characteristic (AUC). During internal validation, the AUC was corrected for overfitting using the bootstrapping method[28] on the dataset, with repetition of the procedure of 500 times. External validation was performed in the LUMC and MST databases. For validation, 100 events of 'admission' and at least 100 non-events were required to occur.[29] Based on admission rates in both LUMC and MST, we considered a validation sample of at least 500 patient visits to be sufficient for external validation of our model.

The external validity was examined by calibration and discrimination of the model in the validation samples, using calibration plots and the AUC. In the calibration plot, the calculated probability of admission is plotted against the observed admission. The calibration slope is the regression coefficient of the model in which the linear predictor (admission yes or no) is the only parameter. Ideally, the slope is 1.[30,31] The intercept in the plot indicates whether predictions are systematically too high or too low and should ideally be zero.[32]

In the LUMC database, data on whether radiology tests had been performed were not recorded. Therefore, we developed a new model on the data following the same strategy for model development, however, leaving out radiology testing. This alternative model was validated in the LUMC sample.

Subsequently, a score chart was developed based on the regression coefficients fitted on the combined data. Therefore, data on radiology testing were imputed for the LUMC database using multiple imputation. An application was built to calculate the chance on admission to facilitate accessibility of the tool in day-to-day practice.[33]

To aid in the decision whether preparations for admission should be started for a specific patient, a specific cut-off point of chance on admission should be determined to guide this decision. Such a cut-off should be based on sensitivity and specificity and the importance of avoiding false-negatives and false-positives (i.e., taking action in a patient that in the end does not need to be admitted versus taking no action in a patient that does need to be admitted). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a range of possible cut-offs in the combined cohort of the MST and LUMC cohorts were calculated.

All analyses were undertaken using R statistics version 3.1.3 (March 9th, 2015).[34] The foreign library was used to transfer the database from SPSS (version 21) to R.[35] For model development, the lrm function of the rms package was used.[36] Finally, the calibration plot was built using the val.prob.ci function, which is an adjustment to the val.prob function of the rms package. For the application, we used Rstudio.[35]

RESULTS

Participants

The derivation database consisted of 76,663 ED visits between January 2012 and June 2014. Selection on age of 70 and over reduced the number to 5,265 patients who visited the ED 7,606 times. The admission rate was 54%. In the derivation group, 55.8% of the patients were male and the median age was 76 years. The validation dataset consisted of 4,250 patient visits from LUMC, of whom 45% were admitted and 563 patient visits from MST, of whom 71% were admitted (table 1).

Predictors of admission

In the derivation cohort, the strongest predictors of admission were laboratory testing (OR [95% CI]: 13.202 [11.104-15.695], p: < 0.001) and arrival by ambulance (OR [95% CI]: 5.168 [4.389-6.085], p: < 0.001) (table 2). The categories 'referred' and 'arrival by ambulance' in the predictor referral status had similar odds ratios and were therefore combined. The 'immediate' (red) and 'very urgent' (orange) triage groups in the MTS classification were also combined. These adjustments did not alter the model performance.

Model development

Based on the AIC, we included the following parameters in the final model: laboratory testing, body temperature, heart rate, diastolic blood pressure, systolic blood pressure, SpO_2, respiratory rate, referral status, MTS category, and radiology testing, which yielded an AUC of 0.770. Bootstrap resampling decreased the performance by 0.004, resulting in an internally validated AUC of 0.766.

External validation

Patient characteristics in the derivation and validation cohort did not significantly differ, except for admission rates in MST. The univariate effects of the predictors within the validation and derivation cohort were comparable.

However, the OR for MTS classification 'immediate' in the LUMC was higher than in Erasmus MC and MST (OR [95% CI]: 64.526 [15.870-262.350] versus 1.861 [1.408-2.460] versus 3.898 [0.897-16.945], respectively).

Discrimination in the LUMC data showed an AUC of 0.725. The calibration plot showed an intercept of -0.308, reflecting the fact that the overall admission rate was lower (45%) compared to the development cohort. The calibration slope was 0.826 (figure 1). Discrimination in the MST data showed an AUC of 0.797. However, MST had an admission rate of 71 per 100 patient visits, resulting in a calibration intercept of 1.018 and a calibration slope of 0.904 (figure 2).

Table 1. *Patient characteristics in Erasmus MC, LUMC, and MST*

	Derivation group (n = 7,606)	Validation group MST (n = 653)	Validation group LUMC (n = 4,250)
Parameter			
Age (median ± IQR)	76 (73-81)	78 (74-83)	78 (74-83)
Sex (%)			
Male	4,246 (55.8)	325 (49.8)	2,097 (49.3)
Female	3,360 (44.2)	328 (50.2)	2,153 (50.7)
Temperature (%) (°C)			
≤ 35.9	135 (1.8)	29 (4.4)	243 (5.7)
36.0-37.0	3,299 (43.4)	201 (30.8)	1,640 (38.6)
37.1-38.4	1,151 (15.1)	144 (22.1)	873 (20.5)
≥ 38.5	484 (6.4)	37 (5.7)	204 (4.8)
Missing	2,537 (33.4)	242 (37.1)	1,290 (30.4)
Heart Rate (%) (bpm)			
< 50	126 (1.7)	14 (2.1)	59 (1.4)
50-100	5,039 (66.3)	395 (60.5)	2,734 (64.3)
> 100	1,056 (13.9)	79 (12.1)	593 (14.0)
Missing	1,385 (18.2)	165 (25.3)	864 (20.3)
Systolic Blood Pressure (%) (mmHg)			
< 90	168 (2.2)	8 (1.2)	42 (1.0)
90-140	2,730 (35.9)	219 (33.5)	1,478 (34.8)
> 140	3,268 (43.0)	236 (36.1)	1,789 (42.1)
Missing	1,440 (18.9)	190 (29.1)	941 (22.1)
Diastolic Blood Pressure (%) (mmHg)			
< 60	819 (10.8)	64 (9.8)	317 (7.5)
60-90	4,041 (53.1)	333 (51.0)	2,395 (56.4)
> 90	1,296 (17.0)	66 (10.1)	598 (14.1)
Missing	1,450 (19.1)	190 (29.1)	940 (22.1)
Respiratory Rate (%) (x/min)			
< 12	339 (4.5)	0 (0.0)	69 (1.6)
12-20	2,091 (27.5)	244 (37.4)	1,612 (37.9)
> 20	254 (16.9)	56 (8.6)	713 (16.8)
Missing	3,893 (51.2)	353 (54.1)	1,856 (43.7)
Oxygen Saturation (%) (%)			
≤92	528 (6.9)	64 (9.8)	210 (4.9)
93-97	3,130 (41.2)	210 (32.2)	1,323 (31.1)
≥ 98	2,246 (29.5)	207 (31.7)	1,764 (41.5)
Missing	1,702 (22.4)	172 (26.3)	953 (22.5)
Laboratory testing (%)			
Yes	6,217 (81.7)	531 (81.3)	963 (22.7)
No	1,389 (18.3)	122 (18.7)	3,287 (77.3)
Radiology testing (%)			
Yes	4,302 (43.4)	207 (31.7)	NA
No	3,304 (56.6)	446 (68.3)	NA
Arrival (%)			
Self-referral	1,127 (14.8)	30 (4.6)	886 (20.8)
Referred	4,119 (54.2)	501 (76.7)	1,901 (44.7)
Ambulance	2,106 (27.7)	105 (16.1)	1,458 (34.3)
Other	254 (3.3)	17 (2.6)	5 (0.1)
MTS classification (%)			
Immediate/Red	255 (3.4)	22 (3.4)	102 (2.4)
Very urgent/Orange	932 (12.3)	119 (18.2)	1,339 (31.5)
Urgent/Yellow	3,851 (50.6)	410 (62.8)	1,908 (44.9)
Standard/Green	1,592 (20.9)	98 (15.0)	877 (20.6)
Non-urgent/Blue	11 (0.1)	4 (0.6)	17 (0.4)
Missing	965 (12.7)	0 (0.0)	7 (0.2)

Table 2. *Univariate logistic regression on outcome admission. For every parameter p-values are shown. Both OR and 95% CI for every category within a parameter were calculated. *Only eight entries of systolic blood pressure were below 90 mmHg. Therefore, the categories within this parameter were reduced to three categories (≤ 140, > 140, missing mmHg).*

	Derivation group (n = 7,606)		Validation group MST (n = 653)		Validation group LUMC (n = 4,250)	
Parameter	**Odds Ratio (OR) [95%CI]**	**P-value**	**Odds Ratio (OR) [95%CI]**	**P-value**	**Odds Ratio (OR) [95%CI]**	**P-value**
Age/10	1.127 [1.045-1.216]	0.002	1.158 [0.882-1.519]	0.290	1.134 [1.103-1.248]	0.010
Sex		0.381		0.338		0.004
Female	0.960 [0.877-1.051]		0.848 [0.604-1.189]		0.839 [0.743-0.947]	
Male						
Temperature (°C)		< 0.001		< 0.001		< 0.001
≤ 35.9	1.999 [1.347-2.967]		2.015 [0.668-6.074]		1.676 [1.274-2.205]	
36.0-37.0	Ref.		Ref.		Ref.	
37.1-38.4	1.339 [1.163-1.541]		1.336 [0.791-2.254]		1.293 [1.096-1.524]	
≥ 38.5	4.942 [3.724-6.559]		11.605 [1.550-86.867]		8.76 [5.617-13.667]	
Missing	0.318 [0.285-0.354]		0.400 [0.266-0.603]		0.406 [0.347-0.475]	
Heart Rate (bpm)		< 0.001		< 0.001		< 0.001
< 50	0.910 [0.637-1.300]		0.655 [0.200-2.142]		1.258 [0.748-2.115]	
50-100	Ref.		Ref.		Ref.	
> 100	1.466 [1.274-1.687]		4.912 [1.745-13.825]		1.743 [1.451-2.094]	
Missing	0.229 [0.201-0.263]		0.170 [0.115-0.253]		0.180 [0.148-0.220]	
Systolic Blood Pressure (mmHg)		< 0.001		< 0.001		< 0.001
< 90	1.253 [0.902-1.741]		*		7.437 [2.64-20.945]	
90-140	Ref.		Ref.		Ref.	
> 140	0.931 [0.839-1.032]		0.595 [0.366-0.967]		0.782 [0.681-0.898]	
Missing	0.227 [0.197-0.261]		0.127 [0.079-0.204]		0.156 [0.127-0.190]	
Diastolic Blood Pressure (mmHg)		< 0.001		< 0.001		< 0.001
< 60	1.673 [1.423-1.966]		5.122 [1.559-16.829]		2.148 [1.668-2.765]	
60-90	Ref.		Ref.		Ref.	
> 90	1.159 [1.020-1.318]		1.027 [0.529-1.993]		0.952 [0.796-1.139]	
Missing	0.259 [0.226-0.295]		0.195 [0.132-0.289]		0.184 [0.152-0.223]	
Respiratory Rate (x/min)		< 0.001		< 0.001		< 0.001
< 12	1.197 [0.943-1.519]		**		0.870 [0.537-1.409]	
12-20	Ref.		Ref.		Ref.	
> 20	1.459 [1.260-1.689]		6.612 [1.557-28.082]		2.072 [1.721-2.495]	
Missing	0.540 [0.485-0.602]		0.373 [0.255-0.545]		0.419 [0.364-0.481]	
Oxygen Saturation (%)		< 0.001		< 0.001		< 0.001
≤92	1.823 [1.483-2.242]		3.758 [1.429-9.882]		3.700 [2.627-5.212]	
93-97	1.118 [1.001-1.248]		1.649 [1.014-2.680]		1.127 [0.977-1.300]	
≥ 98	Ref.		Ref.		Ref.	
Missing	0.313 [0.274-0.358]		0.224 [0.144-0.348]		0.228 [0.188-0.275]	
Laboratory testing		< 0.001		< 0.001		< 0.001
Yes	13.202 [11.104-15.695]		10.886 [6.935-17.087]		12.138 [9.667-15.241]	
No	Ref.		Ref.		Ref.	
Radiology testing		< 0.001		< 0.001		
Yes	2.027 [1.849-2.223]		2.414 [1.696-3.437]		***	
No	Ref.		Ref.			
Arrival		< 0.001		< 0.001		< 0.001
Self-referral	Ref.		Ref.		Ref.	
Referred	4.559 [3.920-5.303]		5.957 [2.664-13.322]		1.314 [1.114-1.550]	
Ambulance	5.168 [4.389-6.085]		9.333 [3.736-23.318]		2.204 [1.856-2.617]	
Other	3.218 [2.427-4.266]		3.333 [0.963-11.542]		2.719 [0.452-16.359]	
MTS classification		< 0.001		< 0.001		< 0.001
Immediate/Red	1.861 [1.408-2.460]		3.898 [0.897-16.945]		64.526 [15.870-262.350]	
Very urgent/Orange	1.840 [1.575-2.149]		4.765 [2.336-9.719]		1.958 [1.698-2.256]	
Urgent/Yellow	Ref.		Ref.		Ref.	
Standard/Green	0.362 [0.320-0.409]		0.236 [0.149-0.375]		0.317 [0.262-0.383]	
Non-urgent/Blue	0.427 [0.125-1.460]		0.130 [0.013-1.262]		0.277 [0.079-0.965]	
Missing	0.820 [0.711-0.944]		****		0.215 [0.026-1.790]	

**None of the patients at MST had a respiratory rate below 12. ***LUMC did not possess any data on radiology testing.
****MST had no missing values in the MTS classification. Ref. = reference category.

Figure 1. *Calibration plot LUMC. Comparison of the predicted probabilities and the observed outcome in the LUMC. The diagonal line is the reflection of the ideal situation (predicted probability = observed outcome). The dashed line is the non-parametric relation between the observed and predicted probability. The triangles represent the deciles of the predicted probabilities in the validation set (n = 4,250). The lower part of the figure shows a histogram of the predicted probabilities of admitted and not admitted patients. The intercept, calibration slope and AUC in the validation set is presented.*

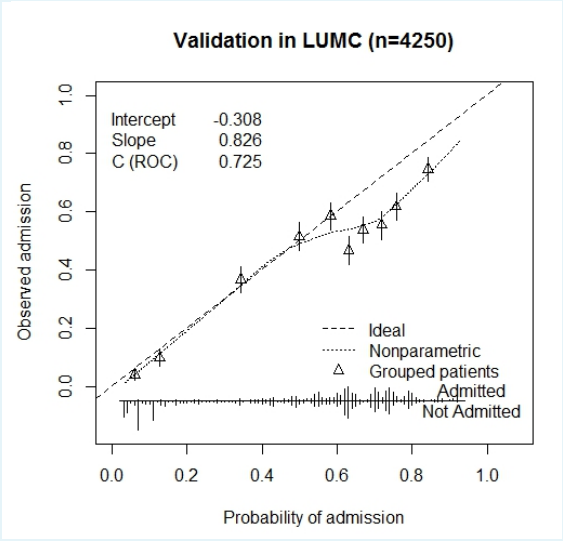

Figure 2. *Calibration plot MST. Comparison of the predicted probabilities and the observed outcome in the MST. The diagonal line is the reflection of the ideal situation (predicted probability = observed outcome). The dashed line is the non-parametric relation between the observed and predicted probability. The triangles represent the deciles of the predicted probabilities in the validation set (n = 653). The lower part of the figure shows a histogram of the predicted probabilities of admitted and not admitted patients. The intercept, calibration slope and AUC in the validation set is presented.*

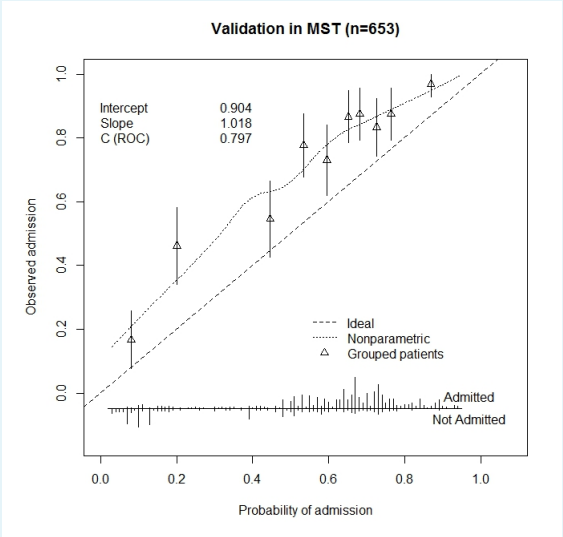

Table 3. *Regression coefficients for the final model*

Parameter	β coefficient	SE	OR
Intercept	-2.3208	0.1072	0.098
Referred			
yes	0.6604	0.0614	1.936
missing	0.5334	0.1457	1.705
Body temperature (°C)			
≤ 35.9	0.1981	0.1153	1.219
36.0-37.0			
37.1-38.4	0.1884	0.0561	1.207
≥ 38.5	1.515	0.1250	4.550
missing	-0.3954	0.0532	0.673
Heart rate (bpm)			
< 50	-0.0670	0.1725	0.935
50-100			
> 100	0.0355	0.0632	1.036
missing	-0.1735	0.1345	0.841
Systolic blood pressure (mmHg)			
< 90	-0.1443	0.1755	0.866
90-140			
> 140	-0.0106	0.0486	0.989
missing	0.4601	0.5922	1.584
Diastolic blood pressure (mmHg)			
< 60	0.5197	0.0787	1.682
60-90			
> 90	0.0809	0.0599	1.084
missing	-0.5494	0.5844	0.577
Respiratory rate (per minute)			
< 12	-0.0880	0.1936	0.916
12-20			
> 20	0.1403	0.0623	1.151
missing	0.0770	0.0499	1.080
Oxygen saturation (%)			
< 92	0.4920	0.0945	1.636
93-97	0.1068	0.0470	1.113
≥ 98			
missing	0.0665	0.0982	1.069
Manchester Triage System			
immediate/very urgent	0.4212	0.0534	1.524
urgent			
standard	-0.4370	0.0583	0.646
not-urgent	-0.3087	0.4642	0.734
missing	0.4022	0.0822	1.495
Laboratory testing			
yes	1.7004	0.0760	5.476
Radiology testing			
yes	0.3735	0.0420	1.453
Non-academic hospital	0.9883		2.687

Formula: Admission chance (%) = 1/(1+exp(-(-2.3208 + Referred + Body temperature + Heart rate + Systolic blood pressure + Diastolic blood pressure + Respiratory rate + Oxygen saturation + Manchester Triage System + (Laboratory testing*1.7004) + (Radiology testing*0.3735) + (Non-academic hospital*0.9883))))

Table 4. *Predictive probability of the CLEARED tool for different admission probabilities*

	All the hospitals combined (%)	95% CI	LUMC	95% CI	MST	95% CI
Admission probability						
60%						
Sensitivity	62.1	60.9-63.3	62.0	59.8-64.2	61.3	56.7-65.8
Specificity	72.4	71.3-73.6	70.3	68.4-72.2	82.1	75.7-87.1
PPV	70.7	69.4-71.8	63.2	61.0-65.4	89.3	85.3-92.4
NPV	64.2	63.0-65.3	69.3	67.4-71.1	46.6	41.1-52.1
Positive tests	45.4	44.5-46.3	44.3	42.8-45.8	48.7	44.8-52.6
70%						
Sensitivity	32.3	31.2-33.5	32.8	30.7-35.0	29.2	25.1-33.6
Specificity	90.1	89.3-90.8	90.2	88.9-91.4	94.7	90.3-97.3
PPV	77.7	76.0-79.2	73.4	70.3-76.3	93.1	87.3-96.5
NPV	55.5	54.5-56.5	62.0	60.4-63.7	35.4	31.3-39.8
Positive tests	21.5	20.8-22.2	20.2	19.0-21.4	22.2	19.1-25.6
80%						
Sensitivity	13.1	12.3-14.0	13.1	11.6-14.7	13.8	10.9-17.4
Specificity	97.9	97.5-98.2	98.5	97.9-98.9	98.4	95.1-99.6
PPV	86.9	84.6-88.9	87.8	83.3-91.2	95.5	86.6-98.8
NPV	51.3	50.4-52.3	58.0	56.4-59.5	31.9	28.2-35.9
Positive tests	7.8	7.3-8.3	6.7	6.0-7.5	10.3	8.1-12.9
90%						
Sensitivity	4.5	4.0-5.0	4.3	3.5-5.4	2.8	1.6-4.9
Specificity	99.5	99.3-99.7	99.7	99.4-99.9	100.0	97.5-100.0
PPV	90.9	87.1-93.7	93.3	85.4-97.2	100.0	71.7-100.0
NPV	49.4	48.5-50.3	55.9	54.4-57.4	29.7	26.2-33.4
Positive tests	2.6	2.3-2.8	2.1	1.7-2.6	2.0	1.1-3.5

Score chart

The final model was named 'CalcuLation of the Elderly Admission Risk in the Emergency Department' (CLEARED) tool and can be used to calculate the probability of admission. We used the parameters from the derivation cohort and introduced a 'hospital factor' to correct for the differences between admission rates of MST (non-academic hospital) and Erasmus MC/LUMC (academic hospital). The formula is presented in table 3; the online application is accessible through the following link: http://bit.ly/clearedtool.

We calculated predictive probabilities of the CLEARED tool of admission for decile cut-off points (table 4). The predictive probabilities for the separate MST and LUMC cohorts were similar, however PPV was higher for MST. This could be explained by the higher admission rate. The positive predictive value ranged from 0.57 to 0.91. This indicates that in the highest decile, 91% of the patients were correctly admitted. An admission cut-off point of 80% would result in the identification of 7.8% (n = 975) who are eligible for earlier admission. Of these patients, 86.9% (n = 847) were actually admitted, meaning that there were 13% unnecessary hospital admissions. Patients with a low admission risk (< 80%) had a similar ED LOS than patients who were admitted with a high admission risk (> 80%). However, patients who were eventually discharged despite a positive advice indicated by the CLEARED tool,

had a significantly longer LOS, median 223 vs. 185 vs. 178 minutes ($p < 0.001$), respectively.

DISCUSSION

The aim of this study was to develop and validate a prediction model for admission for the general elderly population presenting to the ED. We successfully developed the CLEARED tool using data from our retrospective cohort study; a prompt that accurately predicts admission of elderly patients visiting the ED. External validation showed accurate performance. As outlined in the introduction, increased LOS in the ED has detrimental effects on elderly patients. This is not only because the time to adequate treatment is lengthened, but also due to the stay in the ED itself, which enhances the development of a delirious state.[37,38] In our hospital after arrival at the ED, initial evaluation and triage of urgency is performed by a nurse followed by a primary survey of the patient by a physician, followed by diagnostics tests. The decision whether or not to admit the patient to the hospital is made only after the results of the diagnostics are known. Subsequently, a hospital bed request is made and the patient awaits transfer to the ward. In this way, decision-making about admission is late in the process, which causes a marked increase of LOS in the ED.[39] The use of the CLEARED tool can detect elderly patients who are to be admitted to the hospital, shortly after their arrival in the ED. From that moment on, admission to the hospital can be organised without delaying the diagnostic and therapeutic processes. This can dramatically shorten the LOS in the ED for patients. Further reduction of LOS may be possible when using the CLEARED tool in combination with an acute medical unit.

An increasing number of Dutch hospitals have an acute medical unit. In these hospitals, patients who are identified as in need of admission, can be transferred to such a unit where, after the initial diagnostics and therapeutic interventions are performed in the ED, further diagnostics and treatment can be completed. The incorporation of an acute medical unit in addition to the CLEARED tool can further reduce LOS in the ED, which enhances the workflow in the ED and reduces crowding. An acute medical unit is not necessarily a unit, from which every patient gets admitted in-hospital. It can also function as an extension of the ED, allowing observation of patients for several hours, followed by admission or discharge. In our opinion, patients with a high chance of admission according to the CLEARED tool should be admitted to the acute medical unit as early as possible to optimise patient flow through the ED. If admission is not needed – even with a positive CLEARED – they can easily be discharged, which is in line with current practice.

One of the key points of the CLEARED tool is the inclusion of vital parameters as predictors for admission. Using these parameters, we are able to form a better estimate of the severity of illness of a patient, which is the main reason for admission. These parameters are also readily available on arrival at the ED, and are measurements that are routinely performed when patients enter the ED. This makes the CLEARED tool easily applicable.

Another strength of our model is that it is developed using a large database, which reduces the chance of overfitting and limits the uncertainty of the model. Several other prediction models to predict admission have been previously developed. The identification of Seniors at Risk tool (ISAR) is the most well-known screening tool to identify elderly with a high chance of adverse outcomes.[40] This screening tool is composed of six 'yes-no' questions on major topics like cognitive impairment, polypharmacy, and previous hospital admission. The main aim of the ISAR tool is to identify patients at risk of loss-of-functionality after a hospital stay, and not to identify patients at risk of clinical deterioration and death.

The predictors used in the ISAR tool differ vastly from the predictors in our study. In contrast to the CLEARED tool, the ISAR tool focuses on the pre-existing situation before arriving at the ED, in contrast CLEARED, which focuses on vital parameters at presentation. Therefore, gathering information for the ISAR tool takes more time. The discrimination performance of the ISAR for admission ranges from 0.65 [0.62-0.68][41] to 0.68 [0.66-0.70],[42] which is lower than our model.

Similar to the ISAR, is the Triage Risk Screening Tool (TRST), which also comprises of six 'yes-no' questions, such as cognitive and physical impairment, polypharmacy, previous ED visits, and hospitalisation.[43] This model is tested for admission in two studies and performed with an AUC of 0.64 and 0.66, respectively.[42,43] Other admission prediction tools for elderly are triage based (AUC = 0.73, 0.77, 0.741),[44-46] the Silver Code (AUC = 0.63),[41] and a tool derived by Yip et al. (AUC = 0.713).[47] Unfortunately, many of these models have not been externally validated.

The higher AUC of our tool suggests that the CLEARED tool is superior in discrimination, although the AUC is, apart from a measure of model performance, also a reflection of the underlying population. Therefore, a prospective validation study should be performed comparing all the existing tools in one large database. A merit of the external validation of the CLEARED tool was that it was performed in both an academic and a large non-academic teaching hospital. The discrimination remained high in both centres, and calibration was good in the LUMC, but our model underestimated the chance of admission in MST. This was most likely due to the high admission rate (71%) in this centre and possibly a difference in population as it is located in

different part of the country. A factor was introduced to account for the fact it is a non-academic teaching hospital, although we were unfortunately unable to confirm this with other non-academic hospitals. We expected that patient characteristics might differ between academic and non-academic hospitals; nonetheless, it is satisfactory that the CLEARED tool performs well in both settings. This makes it more likely that the model can be generalised to other EDs.

When the CLEARED tool is eventually implemented in clinical practice, we recommend that implementation takes place in a stepwise process. First, validation of the model should take place to establish its congruency with local protocol. Next, all caregivers in the ED, especially triage nurses, should be familiar with the model. To make the model better applicable in clinical practice, we developed an online application, which will automatically calculate the chance of admission after measurement of the parameters. To further determine practical applicability and predictive power, a prospective study should be performed.

Our study has several limitations. A general limitation of this study is that the prediction model is developed based on a retrospective database. As a result, not all parameters that are considered in the model are completely accurate, which could have resulted in biased estimates of the effect of certain predictors. For example, it was not assessed whether oxygen therapy was administered before collecting data on both SpO_2 and respiratory rate. Therefore, the predictive value of these variables is probably underestimated in the CLEARED tool. The need for oxygen therapy on its own could also be an independent predictive variable, however, a prospective study is needed to confirm this. In addition, respiratory rate was only recorded in just more than half of patient entries. An explanation for this could be that the respiratory rate was only measured when the patient was already in a more severe condition. The predictive value of respiratory rate as an independent variable should be evaluated more in future study.

Inevitably, there were many missing values. In order to deal with missing values and prevent losing data, missing values were categorised in a separate group. Using this method, the model can always be applied, even when not all parameters are recorded.

In conclusion, the CLEARED tool can accurately predict admission in the elderly. It proved to exceed the performance of comparable tools. However, further research is needed to implement the tool and to evaluate the effect of the CLEARED tool on LOS and crowding in the ED, length of hospitalisation, and mortality.

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PRESENTATIONS

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ABBREVIATIONS

AIC	Akaike Information Criterion	MD	Medical Doctor
AVPU	Alert Verbal Pain Unresponsive	MST	Medisch Spectrum Twente
AUC	Area Under the receiver operating Curve	mmHg	millimeter Mercury pressure
BSc	Bachelor of Science	min	minute
bpm	beats per minute	MEWS	Modified Early Warning Score
CLEARED	CalcuLation of the Elderly Admission Risk in the Emergency Department	NPV	Negative Predicting Value
CI	Confidence Interval	NA	Not Applicable
df	degrees of freedom	OR	Odds Ratio
ED	Emergency Department	SpO2	Peripheral Oxygen Saturation
ESI	Emergency Severity Index	PPV	Positive Predicting Value
Erasmus MC	Erasmus Medical Center Rotterdam	ROC	Receiver Operating Characteristic
GCS	Glasgow Coma Scale	rms	regression modelling strategies
ISAR	Identification of Seniors At Risk	RR	Respiratory Rate
LUMC	Leiden University Medical Centre	SD	Standard Deviation
LOS	Length Of Stay	SPSS	Statistical Package for the Social Sciences
LRχ2	Likelihood Ratio chi squared	TRST	Triage Risk Screening Tool
lrm	logistic regression model	UK	United Kingdom
MTS	Manchester Triage System	USA	United States of America

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ORIGINAL ARTICLE

Liver stiffness improvement in hepatitis C patients after successful treatment

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ABSTRACT

Background: Successful treatment of chronic hepatitis C with direct-acting antiviral agents (DAAs) is expected to lead to improvement in liver fibrosis in most of the patients. However, limited data are available on the improvement of advanced liver fibrosis and cirrhosis, measured by transient elastography after treatment. This study assessed the change in liver stiffness measurements after successful treatment with DAAs in patients with pre-treatment advanced fibrosis or cirrhosis.

Methods: This observational retrospective cohort study included 514 mono-infected chronic hepatitis C patients, treated with all possible DAA-regimes in the Amsterdam region, the Netherlands. Liver stiffness was measured using FibroScan® at baseline and during follow-up. Cut-off values for staging liver fibrosis were ≥ 9.5 kPa for advanced fibrosis (F3) and ≥ 14.6 kPa for cirrhosis (F4).

Results: Liver stiffness decreased significantly from a median of 15.6 kPa (IQR 11.4-25.4) to 9.4 kPa (IQR 6.2-17.0) in 197 patients with pre-treated advanced fibrosis or cirrhosis. In 50.3% of these patients, liver stiffness improved to a value fitting with mild to moderate fibrosis (< 9.5 kPa, F0-F2) after successful treatment. Multivariate analysis demonstrated that a pre-treatment FibroScan® value of ≥ 20.0 kPa was associated with persisting advanced fibrosis or cirrhosis after treatment (OR 29.07, $p < 0.001$).

Conclusion: Liver stiffness improves significantly after successful direct-acting antiviral agent treatment in chronic hepatitis C patients with advanced fibrosis or cirrhosis prior to DAA treatment. Long-term outcomes regarding occurrence of hepatocellular carcinoma (HCC) in these patients are required to determine whether they can be safely discharged from HCC surveillance.

KEYWORDS

Chronic hepatitis C, direct-acting antiviral agents, improvement of liver stiffness, liver stiffness measurement, transient elastography.

INTRODUCTION

An acute infection with the hepatitis C virus (HCV) results in a chronic infection in 70-85% of all cases. Worldwide, approximately 71 million individuals are chronically infected.[1] Chronic inflammation can cause liver fibrosis and may ultimately progress into liver cirrhosis with significant morbidity and mortality, which may lead to complications such as hepatic decompensation, liver failure, and hepatocellular carcinoma (HCC).[1-3] The rate of fibrosis progression is associated with various co-factors such as increasing age, high body mass index (BMI), elevated serum alanine aminotransferase (ALT) levels, HCV genotype, concomitant alcohol abuse, and co-infection with hepatitis B virus (HBV), or human immunodeficiency virus (HIV).[4-6]

Transient elastography (FibroScan®) provides a non-invasive measure for liver stiffness which is used to quantitatively assess liver fibrosis. Although FibroScan® is not very accurate for the differentiation between moderate

(F2) and advanced liver fibrosis (F3),[7] it is well-validated to establish patients with no signs of liver fibrosis (F0-F1) and those with cirrhosis (F4).[3,8,9]

To prevent further progression of liver fibrosis in chronic hepatitis C (CHC) patients, eradication of the virus is important. Direct-acting antiviral agents (DAAs) have become widely available with little side effects, a relatively short treatment duration and cure rates above 95%.[10,11] Achieving a sustained virological response (SVR) with DAAs is associated with a significant decrease in liver stiffness as measured by FibroScan®.[12,13] This absolute decrease seemed to be greater in patients with higher pre-treatment liver stiffness values.[12] However, most results are based on liver stiffness measurements (LSM) shortly after end of treatment. Limited data are available about the long-term effect of successful treatment with DAAs on LSM in patients with pre-treatment advanced liver fibrosis or cirrhosis.

The goal of our study was to assess the change in liver stiffness using FibroScan® after successful DAA treatment in patients with CHC mono-infection and pre-treatment signs of advanced liver fibrosis or cirrhosis (FibroScan® ≥ 9.5 kPa).

MATERIALS AND METHODS

Study design and population

In this observational retrospective cohort study, we included mono-infected CHC patients who were successfully treated with DAAs from January 2014 to August 2018 at the Amsterdam University Medical Center (UMC), location Academic Medical Centre (AMC), and Onze Lieve Vrouwe Gasthuis (OLVG), location Oost, both in Amsterdam, the Netherlands. All adult patients who were successfully treated (i.e., achieved SVR) with DAAs for their chronic Hepatitis C Virus (HCV) infection with an available FibroScan® result prior to treatment and during follow-up were included. Exclusion criteria were co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (positive Hepatitis B surface Antigen), concomitant liver diseases (such as primary sclerosing cholangitis, haemochromatosis, or auto-immune hepatitis), and a medical history of hepatocellular carcinoma (HCC).

Data collection

Medical record data were retrospectively collected. The following baseline characteristics were collected: age at onset of DAA treatment, gender, ethnicity, HCV genotype, body mass index (BMI), excessive alcohol use (defined as ≥ 4 alcohol units (50 gram) per day), and comorbidities such as diabetes mellitus. Laboratory values at baseline and 12 to 24 weeks after end of treatment (EOT) were collected, including HCV-RNA, liver enzymes, and platelet count. Alanine aminotransferase test (ALT) levels were quantified by automated techniques at each participating centre. The upper limit of normal (ULN) for ALT were ≥ 34 U/ml for female and ≥ 45 U/ml for male. SVR was defined as an undetectable HCV-RNA 12 to 24 weeks after EOT.

Assessment of liver stiffness

Liver stiffness was evaluated using transient elastography, FibroScan® (Echosens, France). Liver stiffness measurements at baseline and at one or more time points during follow-up were collected. Staging of liver fibrosis was based on the following cut-off values: ≤ 7.0 kPa for F0-F1 (no or mild fibrosis), 7.1 to 9.4 kPa for F2 (moderate fibrosis), 9.5 to 14.5 kPa for F3 (advanced fibrosis), and ≥ 14.6 kPa for F4 (cirrhosis).[9] In clinical practice, FibroScan® was not repeated after successful treatment in patients with no signs of fibrosis using FibroScan® prior to treatment. Therefore, only patients with baseline FibroScan® ≥ 9.5 kPa were included and categorised according to the baseline value into three groups: FibroScan® 9.5-14.5 kPa; FibroScan® 14.6-19.9 kPa; and FibroScan® ≥ 20.0 kPa. Patients without available FibroScan® measurements during follow-up were excluded from the analysis. Follow-up measurements after SVR were categorised from 0 to 24 weeks (FS0-24) after EOT, 24 to 100 weeks (FS24-100) after EOT and > 100 weeks after EOT (FS > 100).

For quantification of hepatic steatosis, CAP (controlled attenuated parameter; dB/m) measurements were obtained at baseline and during follow-up.

Primary outcome

Change in liver stiffness measure (LSM) using FibroScan®, expressed as value in kPa and its corresponding fibrosis grade (F0-F4), after achieving SVR in patients with baseline FibroScan® value ≥ 9.5 kPa (F3-F4).

Secondary outcome

To define characteristics of patients with an improved LSM from ≥ 9.5 kPa pre-treatment to < 9.5 kPa after successful DAA treatment.

Statistical analysis

Graphic representation of the results was performed using Graph Pad Prism version 7 for Windows (GraphPad Software, San Diego, California, USA). Statistical analysis was performed using IBM SPSS for Windows version 24.0 (SPSS Inc., Chicago, Illinois, USA). Data was analysed using chi-squared test, Fisher's exact test, Mann-Whitney U test, Wilcoxon signed-rank test, and student's t-test where appropriate. Univariate and multivariate logistic regression was used to estimate odds ratios (ORs) for persisting advanced fibrosis, defined as a liver stiffness value ≥ 9.5 kPa at follow-up. The risk factors

included were thrombocytopenia at baseline, baseline LSM values, baseline LSM value ≥ 20.0 kPa, diabetes mellitus, ethnicity, and HCV genotype. Pearson's or Spearman's correlation were used to test the presence of correlation. Differences were considered statistically significant when $p < 0.05$.

RESULTS

Baseline characteristics

A total of 514 patients with CHC were treated with DAAs in our hospitals between January 2014 to August 2018, of whom 197 (38.3%) had an LSM value ≥ 9.5 kPa at baseline and at least one available LSM during follow-up. In these 197 patients, the median LSM value prior to treatment was 15.6 kPa (IQR 11.4-25.4). At baseline, 90 patients had a LSM of 9.5 to 14.5 kPa; 36 patients had a score of 14.6 to 19.9 kPa; and 71 patients had a LSM of ≥ 20.0 kPa. Median follow-up time after EOT was 36 months (IQR 29-42). The baseline characteristics are shown in table 1. Follow-up measurements were available in 96 patients at FS0-24, in 127 patients at FS25-100, and in 60 patients at FS > 100. In 42 patients, the value at FS > 100 was the second or third FibroScan® measurement during follow-up.

Change in LSM

A statistically significant decrease in LSM was observed both in the whole group as well as in different subgroups (figure 1 and table 2) after successful treatment. Compared with baseline LSM, a median decrease of 5.7 kPa was observed at FS0-24, of 5.9 kPa at FS 25-100, and a decrease of 6.3 kPa at FS > 100. The median difference in all

Table 1. *Baseline characteristics of all patients with pre-treatment LSM ≥ 9.5 kPa (advanced liver fibrosis or cirrhosis, F3 or F4)*

Baseline characteristics (n = 197)		
Gender (male)	n (%)	148 (75.1%)
Age at start treatment (years)	mean ± SD	56 ± 9
BMI (kg/m²)	mean ± SD	26.1 ± 4.2
Diabetes mellitus	n (%)	37 (18.8%)
Ethnicity	n (%)	
Caucasian		107 (54.3%)
Middle Eastern/Northern African		38 (19.3%)
Other/unknown		52 (26.4%)
HCV genotype	n (%)	
Genotype 1		101 (51.3%)
Genotype 2		17 (8.6%)
Genotype 3		47 (23.9%)
Genotype 4		32 (16.2%)
LSM by FibroScan® (kPa)	median (IQR)	15.6 (11.4-25.4)
F3	n (%)	90 (45.7%)
F4		107 (54.3%)
Excessive alcohol use†	n (%)	
Current		16 (8.1%)
Former		38 (19.3%)

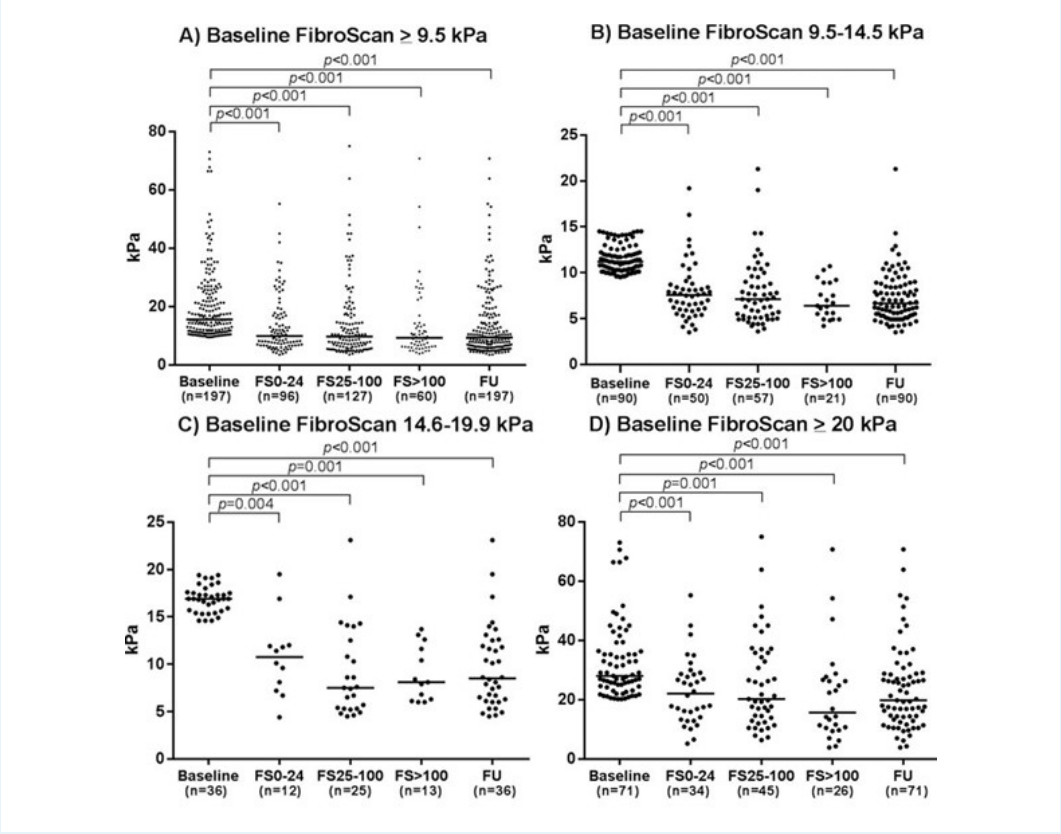
BMI = body mass index; HCV = hepatitis C virus; IQR = interquartile range; LSM = liver stiffness measurements; n = number; SD = standard deviation.
† Excessive alcohol use is defined as ≥ 4 alcohol units (50 gram) per day. Former use is defined as a known history of excessive alcohol use but current use < 4 units per day.

Table 2. *Change in LSM during follow-up*

	N	Baseline	FS0-24	FS25-100	FS > 100	Last available†
FibroScan® baseline ≥ 9.5 kPa (kPa) (median, IQR)	197	15.6 (11.4-25.4)	9.9 (6.7-17.1)* (n = 96/197)	9.7 (6.2-17.3)* (n = 127/197)	9.3 (6.2-14.1)* (n = 60/197)	9.4 (6.2-17.0)*
FibroScan® baseline 9.5-14.5 kPa (kPa) (median, IQR)	90	11.2 (10.3-12.5)	7.6 (6.0-8.7)* (n = 50/90)	7.1 (5.1-9.6)* (n = 57/90)	6.4 (5.2-8.9)* (n = 21/90)	6.6 (5.3-8.7)*
FibroScan® baseline 14.6-19.9 kPa (kPa) (median, IQR)	36	16.9 (15.6-17.6)	10.8 (7.4-12.0)* (n = 12/36)	7.5 (5.3-13.3)* (n = 25/36)	8.1 (6.2-12.1)* (n = 13/36)	8.5 (6.2-12.4)*
FibroScan® baseline ≥ 20.0 kPa (kPa) (median, IQR)	71	28.0 (24.2-36.4)	22.1 (13.9-28.8)* (n = 34/71)	20.2 (13.4-35.8)* (n = 45/71)	15.7 (10.3-27.0)* (n = 26/71)	20.2 (13.3-29.1)*

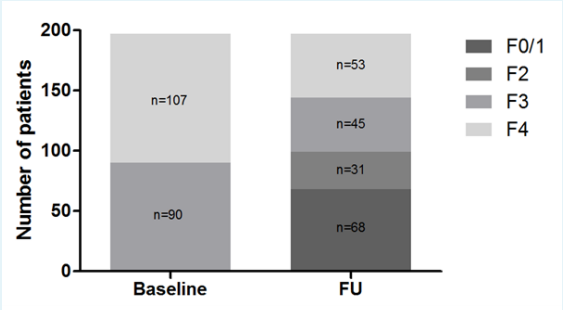
FS0-24 = FibroScan® measurement between 0 and 24 weeks after end of treatment; FS25-100 = FibroScan® measurement between 25 and 100 weeks after end of treatment; FS > 100 = FibroScan® measurement more than 100 weeks after end of treatment; IQR = interquartile range; LSM = liver stiffness measurements; n = number.
† Last available FibroScan® value during follow-up per patient.
* Significant decline ($p < 0.05$) compared to baseline FibroScan® using Wilcoxon Signed Rank test.

Figure 1. *Change in liver stiffness measurements (kPa) according to baseline LSM measurements during follow-up at different time points*



LSM measurements at baseline and at one or more time points during follow-up. The dots represent the LSM of individual patients at each time point. The line represents the median value. Corresponding p-value (Wilcoxon Signed Rank test) represents change in LSM per time point compared to baseline.
A) Change in LSM in all patients with baseline LSM ≥ 9.5 kPa (n = 197).
B) Change in LSM in patients with baseline LSM 9.5-14.5 kPa (n = 90).
C) Change in LSM in patients with baseline LSM 14.6-19.9 kPa (n = 36).
D) Change in LSM in patients with baseline LSM ≥ 20.0 kPa (n = 71).
FS0-24 = FibroScan® measurement between 0 and 24 weeks after end of treatment; FS25-100 = FibroScan® measurement between 25 and 100 weeks after end of treatment; FS > 100 = FibroScan® measurement more than 100 weeks after end of treatment; FU = Last available FibroScan® measurement during follow-up; n = number.

Figure 2. *Change in fibrosis score according to baseline LSM values during follow-up*



LSM, expressed as fibrosis score F0-F4, at baseline and at the last available FibroScan® value per patient during follow-up in patients with baseline LSM ≥ 9.5 kPa.
FU = Last available FibroScan® measurement during follow-up; n = number.

patients between baseline LSM and last available LSM during follow-up was 5.7 kPa (IQR 3.0-9.3). This led to an improvement to mild to moderate fibrosis (LSM < 9.5 kPa) in 50.3% (n = 99) of the 197 included patients (figure 2). Moreover, in 24.3% (n = 26) of the patients with LSM compatible with probable cirrhosis at baseline (≥ 14.6 kPa, F4), LSM improved to values compatible with F0-F2 (< 9.5 kPa). In 15.9% (n = 17) of these patients, LSM even normalised (≤ 7.0 kPa, F0-1). In patients with a pre-treatment LSM ≥ 20.0 kPa (n = 71), only 8.5% (n = 6) improved to LSM values compatible with mild to moderate fibrosis (F0-F2). Progression of LSM was observed in only 21 of the 197 patients (10.7%), with a median progression from 26.3 kPa (IQR 17.6-35.8) at baseline to 32.9 kPa (IQR 22.2-49.3) at the last available LSM during follow-up.

Table 3. *Characteristics of patients (n = 197) with FibroScan® value compatible with advanced fibrosis or cirrhosis at baseline during follow-up: improvement versus no improvement*

		F0-F2 after treatment (n = 99)	F3-F4 after treatment (n = 98)	p-value†
Gender (male)	n (%)	67 (67.7%)	81 (82.7%)	0.015
Age at start treatment (years)	mean ± SD	54 ± 9	57 ± 8	NS
BMI (kg/m²)	mean ± SD	25.5 ± 4.0	26.6 ± 4.3	NS
Diabetes mellitus	n (%)	12 (12.1%)	25 (25.5%)	0.016
Ethnicity	n (%)			
Caucasian		63 (63.6%)	44 (44.9%)	0.006
Middle Eastern/ Northern African		11 (11.1%)	27 (27.6%)	0.008
Other/unknown		25 (25.3%)	27 (27.6%)	NS
HCV genotype	n (%)			
Genotype 1		58 (58.6%)	43 (43.8%)	0.039
Genotype 2		11 (11.1%)	6 (6.1%)	NS
Genotype 3		21 (21.2%)	26 (26.5%)	NS
Genotype 4		9 (9.1%)	23 (23.5%)	0.006
Baseline LSM (kPa)	median (IQR)	11.9 (10.4-14.6)	24.4 (17.2-33.3)	< 0.001
9.5-14.5 kPa	n (%)	73 (73.7%)	17 (17.3%)	< 0.001
> 14.6 kPa	n (%)	26 (26.3%)	81 (82.7%)	< 0.001
> 20.0 kPa	n (%)	6 (6.1%)	65 (66.3%)	< 0.001
Excessive alcohol use ‡	n (%)			
Current		6 (6.1%)	10 (10.2%)	NS
Former		15 (15.2%)	23 (23.5%)	NS
Laboratory values at baseline				
ALT (U/l)	median (IQR)	81 (51-132)	82 (49-126)	NS
Bilirubin (µmol/l)	median (IQR)	8 (6-11)	10 (8-14)	0.002
Platelet count (x10⁹/l)	median (IQR)	209 (157-250)	137 (95-205)	< 0.001
Thrombocytopenia§	n (%)	19 (19.2%)	-55 (56.1%)	< 0.001
Laboratory values 12-24 weeks after EOT				
ALT (U/l)	median (IQR)	22 (17-31)	27 (21-37)	0.002
Bilirubin (µmol/l)	median (IQR)	7 (6-10)	9 (6-13)	0.008
Platelet count (x10⁹/l)	median (IQR)	201 (164-245)	145 (95-204)	< 0.001
Thrombocytopenia§	n (%)	12/89 (13.5%)	45/84 (53.6%)	< 0.001

ALT = alanine aminotransferase; EOT = end of treatment; HCV = hepatitis C virus; IQR = interquartile range; n = number; NS = not significant; SD = standard deviation
† Chi square, Fisher's exact or Mann Whitney U test.
‡ Excessive alcohol use was defined as ≥ 4 alcohol units (50 gram) per day. Former use was defined as a known history of excessive alcohol use but current use < 4 units per day.
§ Thrombocytopenia was defined as platelet count < 150x10⁹/l.

Table 3 shows the characteristics of patients whose advanced fibrosis or cirrhosis persisted during follow-up (n = 98), compared to the patients who showed an improvement to fibrosis score F0-F2 (n = 99) after successful treatment. Patients whose LSM values remained in a range fitting with fibrosis scores F3 or F4 were more often male, HCV genotype 4, and from Middle Eastern or Northern African descent.

Baseline CAP measurements were available in 121 individuals with a mean CAP of 249.0 dB/m (SD ± 54.5). No significant change was observed during follow-up after treatment. Compared with baseline values, a mean difference of -14.5 dB/m was observed at FS0-24 (SD ± 66.5; n = 49; p = 0.135), of +4.8 dB/m at FS25-100 (SD ± 58.5; n = 81; p = 0.465), and +7.2 dB/m at FS > 100 (SD ± 57.9; n = 35; p = 0.469).

Correlation in LSM and ALT

The median baseline ALT level in all patients was 81 U/ml (IQR 51-126). ALT at 12-24 weeks after EOT was measured in 193 patients and decreased to a median of 24 U/ml (IQR

18-35). When using Spearman's correlation coefficient, there was a significant correlation between change in LSM (between baseline and last available LSM) and change in ALT (between ALT at baseline and 12-24 weeks after EOT) (p = 0.000).

Univariate and multivariate analysis

Univariate analysis (table 4) showed a statistically significant association between persistent LSM values fitting with F3 and F4 fibrosis scores after successful treatment and: male gender, thrombocytopenia at baseline, baseline LSM value (especially ≥ 20 kPa), diabetes mellitus, HCV genotype 1 and 4, and Middle Eastern or Northern African ethnicity. Thrombocytopenia (at baseline and at 12-24 weeks after end of treatment), LSM value at baseline, and baseline LSM ≥ 20 kPa were inter-related. In multivariate analysis, we tested for association between persistent LSM values fitting with advanced liver fibrosis or cirrhosis and: gender, diabetes mellitus, HCV genotype 1 and 4, ethnicity, and baseline LSM ≥ 20.0 kPa. Only baseline LSM value ≥ 20.0 kPa was significantly associated with persisting LSM values fitting with advanced liver fibrosis or cirrhosis (OR 29.07, 95% CI 11.02-76.67, p < 0.001).

Occurrence of HCC

Two patients developed an HCC during follow up (112 and 85 weeks after EOT, respectively). Both patients had pre- and post-treatment LSM values of ≥ 20 kPa.

DISCUSSION

A significant change in LSM from a median of 15.6 to 9.4 kPa was observed in our cohort of 197 patients with pre-treatment signs of advanced liver fibrosis or cirrhosis during a median follow-up of 36 months. In half of these patients, LSM improved to values compatible with mild to moderate fibrosis (< 9.5 kPa). Moreover, in 24.3% of the patients with signs of cirrhosis (≥ 14.6 kPa, F4) at baseline, LSM values improved to values fitting with F0-F2 (< 9.5 kPa). There was no significant change in hepatic steatosis as measured by CAP in our cohort. With a median follow-up of 36 months, our study also shows the long-term effect of successful treatment with DAAs on LSM.

The observed decrease in LSM after successful treatment is in line with previous studies, showing that the largest improvement in LSM is to be expected within the first year of follow-up.[12,14] Rapid decline in LSM possibly correlates with resolution of hepatic inflammation.[15,16] In our cohort, we did find a significant correlation between decline in LSM during follow-up and decline in ALT 12-24 weeks after EOT. Improvement in LSM may also be explained by liver regeneration after viral eradication.[12,17] In our study, we did not have post-treatment histology results to investigate this assumption. Recently, two small retrospective studies compared the results of LSM as measured by FibroScan® with liver biopsy results after SVR in DAA-treated patients.[18,19] One study concluded improvement in LSM is overstated when compared to histologic staging but is confirmed with morphometric analysis (i.e., 46% reduction in fibrosis after SVR),[18] whereas in the other study LSM did not correlate with post-SVR liver biopsy results-although no morphometry was performed.[19] Hence, the presumed beneficial effect of DAA-treatment is mostly based on FibroScan® measurements and not histology-based.[12,13,20,21]

Table 4. *Univariate analysis factors associated with persistent advanced fibrosis or cirrhosis after treatment (≥ 9.5 kPa)*

	P-value†	OR‡	95% CI
Gender (male)	0.016	2.28	1.16-4.45
Thrombocytopenia at baseline§	< 0.001	5.32	2.80-10.09
Baseline LSM (kPa)	< 0.001	1.26	1.18-1.36
LSM baseline ≥ 20 kPa	< 0.001	30.53	12.10-77.05
Diabetes mellitus	0.018	2.48	1.17-5.28
Ethnicity (Middle Eastern/ Northern African)	0.005	3.04	1.41-6.56
HCV genotype 1	0.040	0.55	0.31-0.97
HCV genotype 4	0.008	3.07	1.34-7.03

EOT = end of treatment; HCV = hepatitis C virus; LSM = liver stiffness measurements; OR = Odds Ratio; 95% CI = 95% Confidence interval.
† Logistic regression.
‡ Odds Ratio. Represents the change remaining FibroScan® value of ≥ 9.5 kPa.
§ Thrombocytopenia was defined as platelet count < 150 x 10^9/l.

Achieving SVR with DAAs is associated with a decrease in all-cause mortality and hepatocellular carcinoma.[22] In our cohort of 197 patients, only two patients developed an HCC during follow-up. Both patients had a post-treatment LSM > 20.0 kPa. Despite these positive outcomes after successful treatment of CHC, an important unanswered question is whether patients with a baseline LSM of ≥ 9.5 kPa can be safely discharged if their LSM improves to < 9.5 kPa after successful treatment. The current European guideline (2018) for management of CHC states that patients with LSM < 9.5 kPa prior to treatment initiation can be discharged after viral eradication. HCC surveillance should be continued in all patients with a baseline LSM of ≥ 9.5 kPa, despite successful treatment, although no consensus has been reached on the duration of follow-up.[23] In our study, with a median follow-up duration of 36 months, multivariate analysis indicated that an LSM value ≥ 20 kPa at baseline (OR 29.07, p < 0.001) is associated with persisting high LSM values, and that patients with a baseline LSM < 20 kPa are more likely to improve in LSM to values < 9.5 kPa after successful treatment. However, studies investigating the long-term outcomes regarding occurrence of HCC in these patients are needed to assess whether they can be safely discharged from surveillance.

One of the strengths of our study is the large sample size of CHC patients with signs of advanced liver fibrosis or cirrhosis who underwent follow-up FibroScan® measurements after successful treatment of their CHC. However, this study also has its limitations. A limitation is the retrospective design, resulting in a heterogeneous group regarding follow-up time and the fact that we used FibroScan® and did not have histology from patients. As the influence of fasting on FibroScan® outcome is only recently recognised,[24] it is possible that some baseline FibroScan® values were non-fasting values. This could have caused an overestimation of the decline in LSM during follow-up.

CONCLUSION

We show that LSM decreases in CHC patients successfully treated with DAAs with pre-treatment signs of advanced liver fibrosis or cirrhosis (≥ 9.5 kPa). Moreover, in 50.3% of the patients with a baseline LSM value ≥ 9.5 kPa (F3-F4), liver stiffness improved to < 9.5 kPa (F0-F2), and in 15.9% of patients with pre-treatment signs of cirrhosis (F4), LSM normalised (≤ 7.0 kPa, F0-F1). A baseline LSM value ≥ 20.0 kPa was associated with persisting signs of cirrhosis or advanced liver fibrosis. Furthermore, the consequences of the observed change in LSM regarding occurrence of HCC and liver-related death needs to be further investigated in long-term follow-up studies. Only with such data a reliable advice can be given upon the indication and duration of follow-up and surveillance after successful treatment of CHC with DAAs.

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CONFLICT OF INTEREST STATEMENT

SW has served as a speaker, a consultant, or an advisory board member for AbbVie, Bristol-Myers-Squibb, and Gilead Sciences, and received unrestricted research support from AbbVie, Gilead, ENYO Pharma, and Roche, all outside of the submitted work. LB has served as a speaker, a consultant, and an advisory board member for AbbVie, Bristol-Myers-Squibb, Gilead Sciences, Janssen Therapeutics, Merck/MSD, and Roche. MvdV received consultancy fees paid to his institution from Abbvie, Gilead Sciences, ViiV Healthcare, MSD, and Janssen and received unrestricted research support from Abbvie, Gilead, MSD, and ViiV all outside the submitted work. All other authors: no conflicts declared.

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ORIGINAL ARTICLE

Fendrix® compared to Engerix® in HIV-infected patients nonresponding to initial- and re-vaccination schedule

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ABSTRACT

Background: In HIV-infected patients, the immunogenicity of hepatitis B vaccines is impaired. In this randomised controlled study (RCT), we investigated the effect of Fendrix® versus double-dose Engerix® vaccination in previously non-responsive HIV-infected subjects.
Methods: Patients included those who were HIV-infected and non-responders to a primary (single-dose hepatitis B (HBV) vaccination) and a subsequent double-dose HBV revaccination schedule. Subjects were randomised 1:1 to receive Fendrix® (t = 0, 4, 8, 24 weeks) or double-dose Engerix® (t = 0, 4, 24 weeks) vaccinations. Primary efficacy, defined as anti-HBs response ≥ 10 IU/l, was evaluated at week 28 in both study arms.
Results: A subset of 48 patients non-responsive to HBV vaccination was selected, from a cohort of patients at our institution, who underwent HBV vaccination unsuccessfully either in a previous RCT or through standard care. The anti-HBs ≥ 10 IU/l response rate at week 28 in the Fendrix® arm and the Engerix® arm were 85.7% and 65.0%, respectively (p = 0.09). There was no significant difference between the two used vaccine types in the anti-HBs levels reached. In our institution, the overall response rate after initial standard-dose vaccination schedule and double-dose revaccination in our cohort was 75%. In this study, combining the effects of Fendrix and Engerix resulted in a 75% response rate in the 25% remaining non-responders on initial and double-dose revaccination series. This yielded an absolute 19% increase and an overall response to HBV vaccination in HIV-infected patients of around 94% in our cohort.
Conclusion: These results together, suggest that continuing HBV vaccination in non-responders to a first course of single-dose vaccine and a double-dose revaccination scheme is worth the effort. No superiority of one of the investigated hepatitis B vaccines was shown in this cohort but an appropriate number of patients needed to achieve reliable answers was not achieved.

KEYWORDS

Engerix®, Fendrix®, hepatitis B, HIV, non-responder, vaccination

INTRODUCTION

The higher risk of hepatitis B infection in HIV-infected patients, often with an immune compromised status and a known diminished rate of response to hepatitis B virus (HBV) vaccination,[1-4] affords a tailored vaccination strategy such as double-dosing the HBV vaccination[5,6] or doubling the number of hepatitis B vaccine injections over time.[7,8] For management of vaccine non-responders, there are no exact guidelines. Most studies in literature have found a variable response rate of 74-83% to a second series of vaccinations among non-responders.[9,10] Revaccination of HIV-infected individuals with double doses of commercially available hepatitis B vaccines in non-responders to primary single-dose vaccination also has been successful in 50% of these individuals.[11] The introduction of Fendrix® provides an efficient well-tolerated alternative with superior immunogenicity. Fendrix® contains the adjuvant aluminium phosphate and 3-O-desacyl-4'-monophosphoryl lipid A (a Toll-like Receptor 4 agonist). The immunogenicity of Fendrix® was assessed in several clinical trials in healthy volunteers as well as in pre-haemodialysis and haemodialysis patients.[12-16] Overall, due to the improved adjuvant system, Fendrix® demonstrated higher seroprotection rates and higher

antibody concentrations in all studies. Decline of antibody concentration in haemodialysis patients followed the same course as that shown for other plasma- and yeast-derived HBV vaccines, with a faster decline the first 12 months and a slower decline thereafter. The aim of our study was to investigate the effects of Fendrix® versus Engerix® vaccinations in previously non-responsive HIV-infected subjects in a randomised controlled trial.

PATIENTS AND METHODS

Patients and study design

The study was designed as a two-arm, randomised, open-label pilot study in human immunodeficiency virus (HIV)-infected, hepatitis B virus (HBV)-uninfected subjects, naïve to Fendrix® vaccination. We selected a subset of non-responding patients in the Erasmus Medical Center (MC). These patients came from two cohorts. First, we used a previous multi-centre study initiated by our hospital where a total of 811 patients were vaccinated according to an accelerated schedule (t = 0, 1, 3 weeks) or a standard schedule (t = 0, 4, 24 weeks). About 50% of these patients responded.[1] A total of 144 non-responding patients who were in care at the Erasmus MC subsequently received a double-dose HBV revaccination (t = 0, 4, 8 weeks) with a 51% response.[11] The second cohort comprised of non-responders, not included in previous studies, who received a first single-dose HBV vaccination as part of their standard of care schedule; because of non-response, they were also revaccinated with a double-dose HBV schedule. Patients were vaccinated with 10 mcg HBvaxPro® vaccine or 20 mcg Engerix® vaccine in the primary schedules and 20 mcg HBvaxPro® vaccine in the double-dose schedule. These two vaccines are interchangeable.[17] A total of 48 patients in the non-responding cohort via these two routes were included in this study.

Eligible patients were aged ≥ 18 years, had a CD4+ cell count > 200/mm^3, a negative hepatitis B surface antigen (HBsAg), no antibody to hepatitis B core antigen (anti-HBc), and no antibody to hepatitis B surface antigen (anti-HBs) titres. Exclusion criteria were hepatitis C co-infection, pregnancy, radiation therapy, cytotoxic agents, or any immune modulator treatment. Subjects who fulfilled eligibility requirements were randomised 1:1 to receive Fendrix® (t = 0, 4, 8, 24 weeks, according to the manufacturer) or double-dose Engerix® (t = 0, 4, 24 weeks, standard time schedule) vaccinations intramuscularly in the deltoid region. Blood samples were taken at the 28-week time point for quantitative anti-HBs testing (Abbott ARCHITECT® system). The primary efficacy endpoint was the proportion of responders, defined as the number of patients with anti-HBs titres ≥ 10 IU/l at week 28. Secondary endpoint was a difference in antiHBs titre response between Fendrix® and Engerix®.

Table 1. *Baseline characteristics*

Variable	Fendrix® n = 28	Engerix® n = 20
Age median (range)	50.5 yrs (32-68)	45.5 yrs (31-57)
Male n (%)	22 (78.6)	18 (90)
Body Mass Index n; median (25th-75thpercentile)	27; 26.2 (23.6-30)	20; 26.5 (23.2-30.7)
Nadir CD4+ cell count; median (25th-75thpercentile)	180 (93-248)	195 (53-250)
Start CD4+ cell count; median (25th-75thpercentile)	515 (375-718)	605 (390-800)
Start CD4+ cell count ≤ 200 n (%)	0	0
Start CD4+ cell count 200-500 n (%)	14 (50)	7 (35)
Start CD4+ cell count ≥ 500 n (%)	14 (50)	13 (65)
On cART (%)	27 (96.4)	20 (100)
HIV-RNA < 20 c/ml n (%)	16 (57.1)	7 (85)
HIV-RNA ≥ 20 - ≤ 50 c/ml n (%)	8 (28.6)	2 (10)
HIV-RNA > 50 - ≤ 75 c/ml n (%)		1 (5)
HIV-RNA > 75 - ≤ 250 c/ml n (%)	3 (10.7)	
HIV-RNA 1800 c/ml n (%)	1 (3.6)	

cART = combination antiretroviral therapy; HIV = human immunodeficiency virus; n = number

Statistics

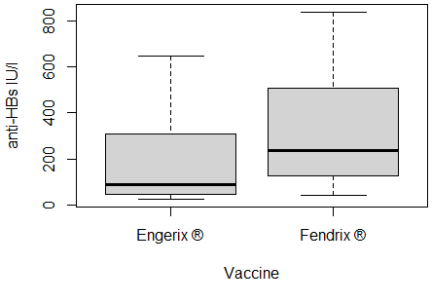
A logistic regression analysis was performed to analyse the primary endpoint. We included vaccine type (reference level was Engerix®) in the model because we wanted to investigate the differences in the outcome between the two arms of the study. In this model, we corrected for other baseline covariates including the HIV-RNA load and CD4 count at study inclusion, nadir CD4, age, and sex. The difference between anti-HBs titre was assessed by Wilcoxon rank sum test.

Approval was obtained from the Medical Ethics Committee of the Erasmus Medical Center (MEC-2010-390) and informed consent was obtained from each patient.

Figure 1. *Statistical Analysis*

A logistic regression was performed to investigate the association of Titer_wk_28_ja_nee with HIVRNA_revacc_code, CD4_revaccTR, nadir_CD4TR, Vaccin, Age and Geslacht

	odds ratio	CI	CI	p-value
(Intercept)	2.2402	0.0155	382.0110	0.7491
HIVRNA_revacc_code	1.1178	0.1915	7.4143	0.9016
CD4_revacc	0.9968	0.9933	0.9998	0.0477
nadir_CD4	1.0011	0.9944	1.0083	0.7443
VaccinFendrix	2.9454	0.5841	18.2953	0.2067
Age	1.0375	0.9322	1.1627	0.5044
Geslachtfemale	0.7278	0.1065	6.3573	0.7497



CI = confidence interval; HIV = human immunodeficiency virus

RESULTS

Forty-eight HIV-infected patients were included in the study. During the course of the study (March 2011 – June 2013), the guidelines on primary HBV vaccination in HIV-infected patients in the Netherlands were changed (December 2012) to a double dose. Therefore, enrolment in the study was prematurely terminated as subsequent patients did not fulfil the inclusion criteria of the study anymore.

Twenty patients received Engerix® and twenty-eight received Fendrix®. All Engerix® patients received three double dosages of the vaccination; all Fendrix® patients received four vaccine doses according to the manufacturer's instructions. Patient characteristics in both groups were similar at baseline. Table 1 reports the distribution of age, gender, body mass index, start CD4+ cell count, nadir CD4+ cell count, usage of combination antiretroviral therapy (cART), and HIV-RNA at start of vaccination. Both groups consisted of mostly males, with similar and current CD4+ cell counts in the normal range and nearly all patients were on cART with a reasonable to excellent viral suppression.

The response rates, defined as anti-HBs ≥ 10 IU/l, at week 28 in the Fendrix® arm and the Engerix® arm were 85.7% and 65.0%, respectively (p = 0.09). A mean 75% responded to either vaccination. As is shown in figure 1, there was no significant difference in the proportion of patients with anti-HBs ≥ 10 between the two used vaccine types if we correct for HIV-RNA at vaccination, CD4+ cell count at vaccination, nadir CD4+ cell count, type of vaccine, age, and gender. In addition, we found no significant difference between anti-HBs titres after vaccination by either vaccine strategy. All included patients received the complete vaccination series. Compliance to the vaccination schedule in the Fendrix® group between the first and fourth vaccine (t = 0 and 24 weeks) was 64.2% (18/28 patients). Of the remaining 10 patients, 2 were vaccinated at week 23, 4 at week 25, 2 at week 26, 1 at week 27, and 1 at week 34. In the Engerix® group, compliance between the first and third vaccine (t = 0 and 24 weeks) was 60% (12/20 patients). Of the remaining 8 patients, 1 was vaccinated at week 22, 1 at week 23, 4 at week 25, 1 at week 26, and 1 at week 50.

DISCUSSION

In our observational study of the effect of Engerix® and Fendrix® revaccination in a previously non-responder group to HBV primary and booster vaccination, we found a response rate of 65.0% and 85.7%, respectively. No superiority of one of the investigated hepatitis B vaccines was shown in this cohort because the number of patients needed for this analysis were not achieved.

HBV vaccination in HIV-infected patients is a challenging opportunity for several reasons. First, the prevalence of HBV infection among men having sex with men (MSM) is high and unprotected sex imposes an increased risk of contracting the disease. Second, adherence to the standard HBV vaccination schedule is a matter of concern and has to be proven difficult in daily practice for both doctor and patient,[18-21] and third, HIV-infected patients have an impaired response and show a wide diversity of seroconversion to HBV vaccination as summarised in the review of Mena et al.[22] With the use of Tenofovir (TDF) as part of a first-line cART regimen in HIV-infected patients, the viral load in treated patients decreases, which

also decreases the risk of HBV transmission. However, considering the latest developments in HIV treatment where non-TDF-containing cART regimens as part of dual treatment or single tablet regimens are prescribed (for example, Dolutegravir/Abacavir/lamivudine, Dolutegravir/Rilpivirine, Dolutegravir/lamivudine) the necessity of effective immunity against HBV is still ongoing.

To our knowledge, only two studies have published data on the effect of Fendrix® as a revaccination strategy in HIV-infected patients. In the study of de Silva et al., 22 patients who had previously not responded to at least one course of standard vaccines showed an overall response rate of 95%.[23] Machiels et al. showed, in a retrospective analysis of 100 patients with HIV and nonresponding to prior HBV vaccination, a seroconversion rate of 81% irrespective of the Fendrix® scheme used or the amount of vaccines given.[24]

In our previous studies, we achieved an overall response rate to HBV vaccination of 75% among HIV-infected patients (around 50% responded on primary single-dose HBV vaccinations and 51% additional success rate was achieved after a double-dose booster HBV vaccination scheme).[11] In this study, a total of 75% patients responded to the Fendrix® or Engerix® vaccinations. This means that an additional 19% of HIV-infected patients responded and thus, all together (primary, booster, and re-booster HBV vaccination), an ultimate overall response to HBV vaccination in HIV-infected patients of around 94% can be achieved. These results suggest that continuing HBV vaccination in non-responders is worth the effort.

Although there was a trend of higher anti-HBs levels in the Fendrix® group responders, there was no significant difference in overall response between the two groups with the data we have collected. We realise that applying a regression model on such a small number of subjects should be done with caution and that no strong conclusions can be made.[25] However, the results can be used for a future study. The number of included HIV-infected patients needed to achieve reliable answers were not achieved due to interruption of the study. Since 2012, Dutch guidelines advise the initiation of a primary vaccination scheme with double-dose HBV vaccination at t = 0, 4, 24 weeks in HIV-infected patients when CD4 count ≥ 350 cells/mm^3, followed by double-dose revaccination at t = 0, 4, 8 weeks in non-responders. Although the effect of the modification of the guideline is not yet studied, we assume that the number of non-responders is decreasing. The changed guidelines made it impossible to include more patients in our Fendrix® versus Engerix® study. As there may be a difference between double-dose HBV vaccination and Fendrix®, it could be interesting to compare these two vaccines as a first vaccination schedule in a randomised controlled trial. While HIV patients on cART in the Netherlands do have repeated visits and are generally compliant, the approach of continuing HBV vaccination until adequate response is less favourable. Primary immunisation series with a more effective vaccine is of great relevance since it would require fewer injections and appointments, thereby reducing the overall cost.

In addition, it is important to realise that our patients belong to a group of non-responders to initial and revaccination schedules. Starting with a strong vaccine in the first schedule and being able to avoid re-vaccination seems reasonable and could be cost saving. Alternatively, our study signals that a third round of HBV vaccination is worth the effort in previous non-responders.

DISCLOSURES

The authors declare that there are no conflicts of interest.

The data from the Fendrix® patients were used in a retrospective multicentre study published in AIDS. 2019 Mar 1;33(3):503-507. doi: 10.1097/QAD.0000000000002085.

For this study, free Engerix® and Fendrix® vaccines were received from GlaxoSmithKline.

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CASE REPORT

Brain lesions in a patient with rectal cancer: mind your step

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ABSTRACT

Cerebral toxoplasmosis is a potentially fatal infection most commonly seen in immunocompromised patients. We present a patient on long-term immunosuppressive therapy after kidney transplantation and a recent history of oligometastatic rectal cancer, with cerebral lesions as a result of toxoplasmosis. Heightened awareness of the occurrence of opportunistic infections in patients with cancer who are taking immunosuppressive drugs is needed among clinicians.

KEYWORDS

Brain lesions, brain metastases, cerebral toxoplasmosis, immunocompromised patients, magnetic resonance imaging scan

INTRODUCTION

Toxoplasma gondii is a parasitic infection that mostly causes symptomatic disease in immunocompromised individuals including those with HIV/AIDS, cancer, and transplant recipients. The seroprevalence of antibodies to *T. gondii* varies substantially among different geographic locales, ranging from approximately 11% in the United States to more than 80% in certain European, Latin American, and African countries.[1] Symptomatic disease in immunosuppressed individuals most often occurs as a result of reactivation of latent infection.[2] Thus, the seroprevalence among immunocompromised patients generally mirrors the rate of seropositivity in the general population.[3] The most common clinical presentation of toxoplasmosis in immunocompromised patients is cerebral toxoplasmosis.[1] In the majority of patients with cerebral toxoplasmosis, therapy is initiated after making a presumptive diagnosis based on clinical symptoms, radiographic features, and serology. We present an immunocompromised patient with a history of recent oligometastatic rectal cancer with brain lesions, leading to a diagnostic and therapeutic challenge.

CASE REPORT

In May 2018, a 66-year-old woman was diagnosed with cT3N0 rectal cancer with synchronous oligometastatic liver disease. Treatment was initiated with curative intent and consisted of neoadjuvant chemotherapy, followed by laparoscopic abdominoperineal resection and microwave ablation of the liver metastasis. Her medical history was remarkable for end-stage renal disease, for which she received a living unrelated donor kidney transplantation in 2003 and immunosuppressive therapy. She was taking mycophenolate mofetil 750 mg twice daily and prednisone 5 mg daily at presentation.

In March 2019, a positron emission tomography computed tomography scan was performed for oncological follow up, which showed oligometastases in the lung (three lung nodules). Henceforth, stereotactic radiotherapy with curative intent was planned. Two months later, the patient presented with progressive right-sided weakness and aphasia. Physical examination on presentation revealed right-sided hemiparesis with ipsilateral hypaesthesia, gait instability, and expressive dysphasia. MRI scan of the brain showed a ring-enhancing lesion in the left thalamus (figure 1). Initially the neurologists suspected metastatic disease. However, after discussing the patient's case in the neuro-oncology multidisciplinary team meeting and considering the full medical history, the differential diagnosis included infectious aetiology in addition to brain metastases. A lumbar puncture was performed and revealed a pleocytosis of 35 leucocytes/µl (reference: 0-5/µl) with increased protein 566 mg/l (reference: 150-450 mg/l) and glucose 7.5 mmol/l (reference: 2.2-3.9 mmol/l) levels. Cerebrospinal fluid (CSF) cytology showed no evidence of

malignant cells. Serological tests demonstrated positive serum anti-toxoplasma IgM antibodies (index: > 10,000) and anti-toxoplasma IgG antibodies (titre: 44 IU/ml) with an intermediate IgG avidity. *Toxoplasma gondii* polymerase chain reaction (PCR) test in the CSF was positive. After six weeks, the serological tests were repeated and showed a greater than four-fold rise in IgG antibody titre (titre: 182 IU/ml), which supported an acute infection.[4] A brain biopsy was considered, but eventually not performed given the risk of the procedure and the presumptive diagnosis of cerebral toxoplasmosis on clinical, radiological, and serological basis. The patient was treated with pyrimethamine 50 mg daily, sulfadiazine 1000 mg four times per day, and folic acid 15 mg daily for six weeks according to guidelines.[1] Initially, there was improvement of the neurological symptoms. However, repeat MRI scan of the brain in June 2019, four weeks after initiation of therapy, showed an increase of the thalamic lesion and multiple new nodular lesions throughout the brain (figure 2). Three weeks after completing the therapy in July 2019, there was significant clinical improvement in the dysphasia and motor strength of the right leg. MRI scan showed a

Figure 1A. *April 2019, before start of therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the brain shows a ring-enhancing lesion in the left thalamic region with an eccentric "target sign" suggestive of toxoplasmosis.

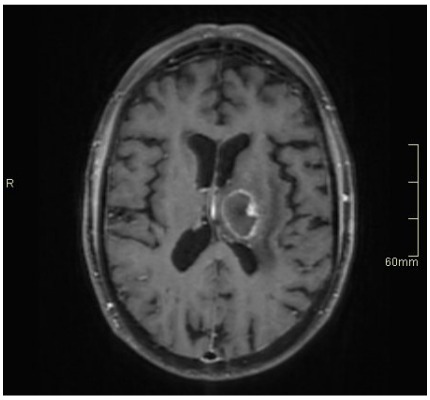


Figure 1B. *April 2019 (cerebellum), before start of therapy.*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the cerebellum shows no lesions.

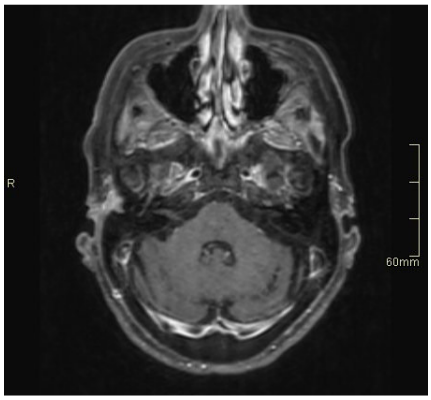


Figure 2. *June 2019, four weeks after start of therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the brain shows progressive disease with an increase in diameter of the ring-enhancing lesion in the left thalamic region and multiple nodular enhancing lesions spread throughout the brain.

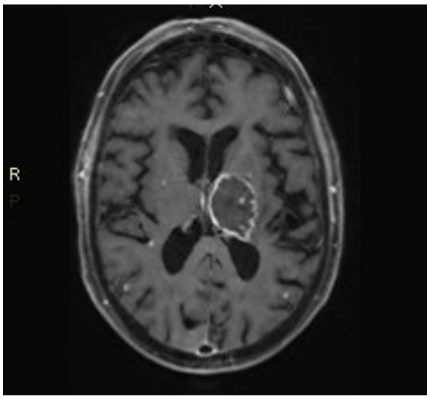


Figure 3. *July 2019, three weeks after completing therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the brain after therapy for toxoplasmosis shows a decrease in the volume of the left thalamic lesion and disappearance of the smaller lesions.

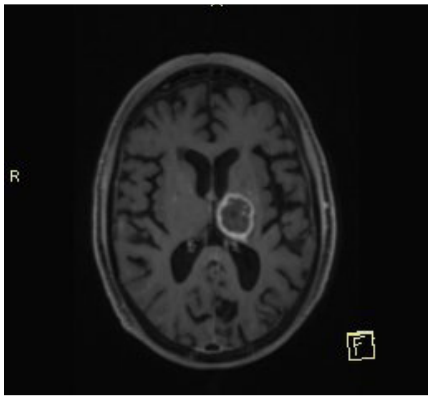


Figure 4. *September 2019, 11 weeks after completing therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the brain shows minimal decrease in the volume of the left thalamic lesion, but multiple small nodular enhancing lesions in the right hemisphere.

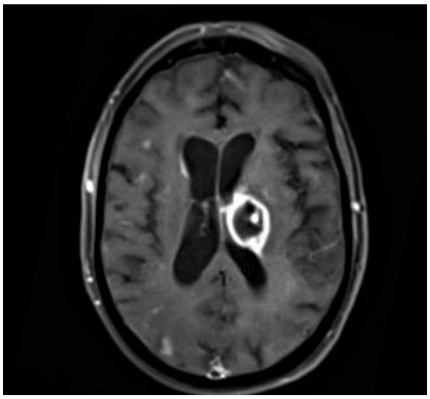


Figure 5A. *November 2019, 5 weeks after restarting therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the brain shows massive nodular and ring-enhancing lesions spread throughout the brain. The lesion in the left thalamic region, suggestive of toxoplasmosis, again decreases in volume.

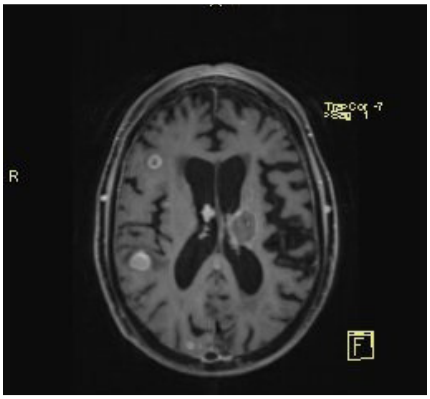
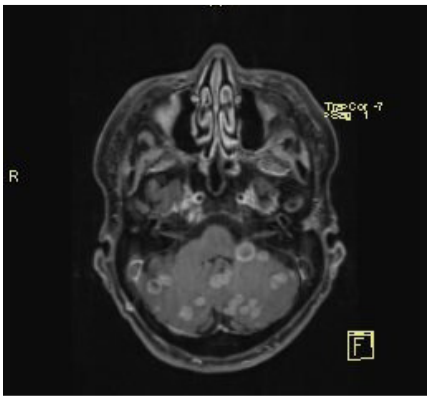


Figure 5B. *November 2019 (cerebellum), 5 weeks after restarting therapy*
Axial T1-weighted, contrast-enhanced, fat-suppressed MRI of the cerebellum shows massive nodular and ring-enhancing lesions spread throughout the cerebellum compared to figure 1B.

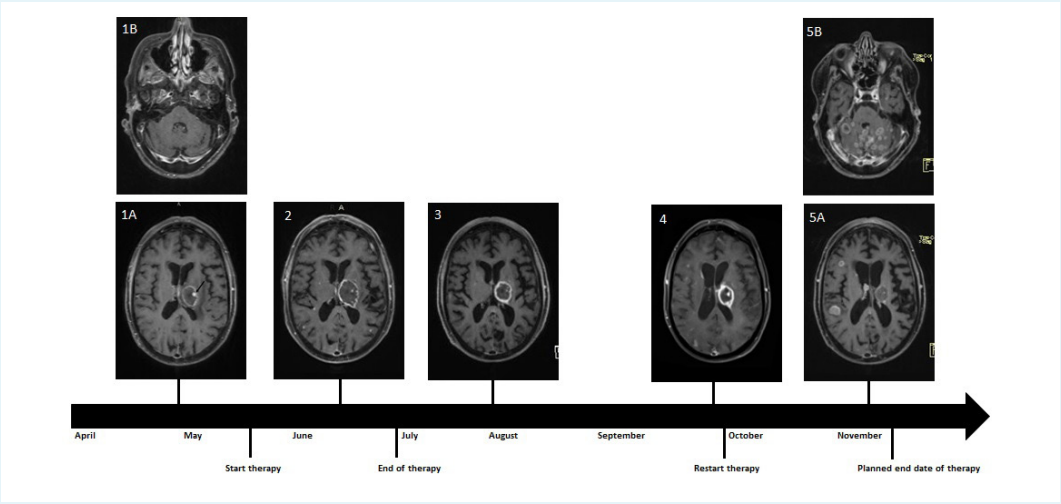


decrease in the thalamic and nodular lesions (figure 3). Despite the permanent immunocompromised state of the patient after completing the six-week therapy, secondary prophylaxis (chronic maintenance therapy) was not given. Approximately two months later, in September 2019, the patient returned with worsening neurological condition and increase of the nodular lesions in the brain (figure 4). It was decided to restart the treatment for cerebral toxoplasmosis for six weeks followed by lifelong secondary prophylaxis. Initially, the patient clinically improved but approximately five weeks later, in November 2019, the patient returned with worsening neurological condition. Repeat MRI scan showed further decrease of the left thalamic lesion, but multiple new lesions throughout the brain, both nodular and ring enhancing, especially in the cerebellum (figure 5). This was suggestive of a combination of cerebral toxoplasmosis and metastatic disease. The patient died shortly after. She never received secondary prophylaxis for toxoplasmosis. Figure 6 shows a timeline of the MRI scans, reflecting the clinical course of the patient as described above.

DISCUSSION

Toxoplasmosis is an infection caused by the intracellular protozoan parasite *Toxoplasma gondii*. In immunocompetent hosts, the infection is usually asymptomatic. In immunocompromised patients though, the infection can be potentially fatal.[5] Here, we present a renal transplant patient on immunosuppressive therapy with symptomatic brain lesions. The patient was initially suspected of having brain metastases because of the recent history of rectal cancer, even though brain metastases from colorectal cancer are rare with an incidence ranging from 0.6 to 3.2%.[6] However, given her deeply immunocompromised state, the differential diagnosis was broadened and a presumptive diagnosis of cerebral toxoplasmosis was made. The diagnosis was further supported because of the clinical and radiological response after initiating therapy for toxoplasmosis. The patient had not received any treatment for the malignancy in the meantime. It should be highlighted that in our case, the patient mistakenly had not received secondary prophylaxis after completing

Figure 6. *Timeline*



her initial therapy. According to guidelines, patients who have completed initial therapy should be given secondary prophylaxis until immune reconstitution occurs or indefinitely, if the patient is permanently immunocompromised.[1] Our patient was permanently immunocompromised given her lifelong immunosuppressive therapy following her kidney transplantation.

An MRI scan is the imaging modality of choice for cerebral toxoplasmosis, however accurate clinical diagnosis based on radiographic features can be difficult as these can overlap with lymphoma and metastatic disease.[7] The distribution of lesions can help discriminate. Metastases are most often located in the cortical or subcortical regions due to haematogenous spread compared to the deep brain nuclei (basal ganglia, thalamus) lesions of toxoplasmosis. Moreover, metastases often start as smaller, solidly-enhancing lesions, before becoming ring-enhancing secondary to necrosis either from outstripping available blood supply or following treatment such as chemotherapy or irradiation.[8] On the last MRI scan of our patient, the lesions in the brain showed a distribution consistent of both toxoplasmosis and metastases. The thalamic lesion had further decreased in size, while the MRI scan showed multiple new lesions throughout the brain as well. The combination of the radiological features, the clinical deterioration despite restarting treatment for cerebral toxoplasmosis, and the fact that the patient had not received any treatment or follow-up for her oligometastatic malignancy during this period were suggestive of additional brain metastases.

In conclusion, this case highlights the difficulties of investigating the aetiology of brain lesions in deeply immunocompromised patients and emphasises the importance of making a broad and complete differential diagnosis taking the full medical history of the patient into consideration. Multidisciplinary team meetings are of importance in this process. Awareness of opportunistic infections may lead to more focused requests for radiologists and discussion in the multidisciplinary team.

DISCLOSURES

The authors declare no conflicts of interests. No funding or financial support was received.

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CASE REPORT

Renal insufficiency due to an orthohantavirus infection in the north of the Netherlands

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KEYWORDS

Nephropathia endemica, orthohantavirus infection, puumala virus

ABSTRACT

We describe a patient with an orthohantavirus infection in the north of the Netherlands. Orthohantavirus cases in the Netherlands are rare and most cases occur in the east of the Netherlands. Orthohantavirus infections should be included in the differential diagnosis in travellers and non-travellers, and patients from areas other than the east of the Netherlands if flu-like symptoms and acute renal insufficiency are present.

What was known on this subject?
Orthohantavirus infections are highly endemic to specific parts of the world.
Different renal manifestations are known with orthohantavirus infections.
Autochthonous orthohantavirus infections in the Netherlands are rare, but occur primarily in the east of the Netherlands.

What does this add?
Orthohantavirus infections may also occur in areas outside the east or south of the Netherlands.
Orthohantavirus infections should be included in the differential diagnosis in a patient with flu-like symptoms and renal manifestations.
A thorough exposure inquiry is important and could prevent the need for a renal biopsy in individual cases.

INTRODUCTION

Orthohantaviruses compromise a group of enveloped RNA viruses of which, over 21, are associated with human disease.[1] Orthohantaviruses are transmitted through rodent hosts, insectivores, and bats. Different hosts carry different orthohantaviruses. An overview of orthohantaviruses found in the Netherlands can be found in table 1 and figure 1.[2-4] Puumala virus is the most common type in the Netherlands, which has been found in bank voles throughout the country and is known to cause human infections, mostly in the east, the region of Twente, and south, the province of Noord-Brabant.[2,3,5] This case report describes a patient with an orthohantavirus infection in Groningen, located in the north of the Netherlands.

Table 1. *Types of orthohantavirus found in the Netherlands*

Virus	Host	Disease
Puumala virus	Bank vole, *M. glaerolus*[1]	NE
Tula virus	Common vole, *M. arvalis*[2]	NE
Seoul virus	Brown rat, *R. norvegicus*[3] and black rat, *R. rattus*	HFRS

NE = nephropathia epidemica; HFRS = haemorrhagic fever with renal syndrome

CASE REPORT

A 38-year-old female was admitted to our hospital in June 2019 with fever and headache since a few days. Physical examination showed no abnormalities. Laboratory analysis

Figure 1. *Host carriers of orthohantaviruses found in the Netherlands. 1. Bank vole; 2. Field mouse; 3. Brown rat.*

Photos by Jelger Herder, www.digitalnature.org

showed a mild renal insufficiency, a thrombocytopenia, and an elevated C-reactive protein (CRP) (table 2). Blood cultures were taken and a chest X-ray was normal. Because of persistent fever cefuroxime was started on the suspicion of a bacterial infection. The acute renal failure was considered a prerenal impairment resulting from dehydration.

One day after hospitalisation, her fever disappeared, and her headache improved under acetaminophen. Antibiotics were discontinued because of persistent negative blood cultures and lack of a proven bacterial infection. However, in contrast to clinical improvement, the patient's renal function deteriorated (table 2). An ultrasound of the kidneys excluded postrenal obstruction. The urinalysis showed no leucocyturia or erythrocyturia but did determine a mild albuminuria. Auto-immune serology showed no abnormalities. Serology, PCR and blood culture for leptospirosis was negative (table 3). On repeated anamnesis, the patient claimed to have cleaned up faecal excrements of mice a few days earlier. The patient reported no recent traveling neither abroad nor to other areas in the Netherlands.

The patient was discharged after a renal biopsy and diagnostics for orthohantavirus on blood was performed, nine days after the first symptoms. At the time of the outpatient clinic visit, the patient's renal function and thrombocytes had been restored to normal. Puumala virus serology turned out to be positive (both IgM and IgG). PCR and blood culture for orthohantavirus was negative. The renal biopsy specimen showed few reactive changes with little increase of monocyte infiltration in the

Table 2. *Laboratory results*

	Day 0 (admittance)	Day 3	Day 4	Outpatient clinic (after 2 months)
Blood tests				
Haemoglobin, normal 7.5-10 (mmol/l)	9.4			
Leucocytes, normal 4.5-10 (x 10^9/l)	8.5			
Thrombocytes, normal 150-400 (x 10^3 per mm^3)	41	101		273
Creatinine, normal 45-80 (µmol/l)	107	153	146	71
Urea, normal 2.5-7.5 (mmol/l)	4.3	8.4	7.9	4.9
CRP, normal < 10 (mg/l)	160	51	38	0.6
Urine analysis				
RBC, normal < 5-10/µl	33			
WBC, normal < 10-20/µl	77			
Albumin excretion (g/day)			0.3	
Creatinine excretion (mmol/day)			10.9	

CRP = C-reactive protein; RBC = red blood cells; WBC = white blood cells

Table 3. *Auto-immune serology and microbiology results*

ANA IgG (IF), titre	1:80
Anti-ds DNA, normal < 15 IU/ml	2.8
ENA screening	Negative
ANCA-PR3, normal < 2 IU/ml	< 0.2
ANCA-MPO, normal < 3.5 IU/ml	< 0.2
Puumala virus IgM (MAT)	Positive, titre > 1000
Puumala virus IgG (MAT)	Positive, titre > 1000
Leptospira Ig (ELISA)	Negative
Leptospira IgM (ELISA)	Negative
PCR *Leptospira* (blood)	Negative
Blood Culture *Leptospira*	Negative

ANA = anti-nuclear antibodies; ANCA =anti-neutrophil cytoplasmic antibodies; ds =double- stranded; ELISA =enzyme-linked immunosorbent assay; ENA =extractable nuclear antigen antibodies; Ig =immunoglobulin; IgM =immunoglobulin M; MAT =microscope agglutination test; MPO =myeloperoxidase; PCR =polymerase chain reaction; PR3 =proteinase 3

interstitium, no signs of a tubulo-interstitial nephritis or glomerulonephritis.

DISCUSSION

Orthohantaviruses are transmitted to humans by aerosols from contaminated excreta of infected rodents. It is thought that the type of orthohantavirus is associated with a specific host species due to co-evolution of the viruses and reservoir hosts.[6]

Orthohantaviruses predominantly infect endothelial cells leading to damage of the vascular barrier, which is the cornerstone of the pathophysiology.[7] This can lead to three clinical syndromes: haemorrhagic fever with renal syndrome (HFRS), nephropathia epidemica (NE), and orthohantavirus cardiopulmonary syndrome (HCPS), depending on the type of orthohantavirus.[1] Orthohantavirus subtypes that cause HCPS are only found in the Americas, due to the distribution of the rodent hosts.

HFRS is caused by the Seoul, Hantaan and Dobrava-Belgrade viruses. The Seoul and Hantaan viruses are transmitted by rats, and the Dobrava-Belgrade virus by the yellow-necked mouse. In the Netherlands, human HFRS cases are only caused by Seoul virus infections transmitted by brown rats.[3,8] The rodent host of the Dobrava-Belgrade virus is present in the Netherlands, but this virus is not known to circulate.[9,10] HFRS starts with a flu-like presentation such as high fever, headache, backache, abdominal pains, nausea, and vomiting. Later, HFRS can lead to haemorrhages such as conjunctival haemorrhages, petechiae, epistaxis, and even intracranial haemorrhages. The earliest and more specific laboratory abnormality is a rapid decline in platelet count. HFRS can lead to renal manifestations like reduced kidney function with oliguria or anuria, proteinuria, and microscopic haematuria.[9] Puumala virus causes NE, a milder form of HFRS. NE is not correlated to haemorrhagic manifestations and shock.[11] Our patient had flu-like symptoms preceding the decrease in kidney function, which fits with the natural course of NE.[12]

In the Netherlands, there is a reporting obligation for orthohantavirus since 2008. The incidence has been low (0.0-0.3 per 100,000, years 2008-2018) with a total of 62 reported autochthonous cases, most of which were Puumala virus infections in Twente.[13] This is slightly lower than the average incidence in Europe overall (0.4-0.8 per 100,000, years 2013-2017). Most of these cases occurred in Finland or Germany.[14] The highest incidence of orthohantavirus (HFRS) is found in China, with a reported incidence of 0.83 per 100,000.[15]

A study in healthy individuals in the Netherlands showed a seroprevalence of 1.7% with the highest rate of 3.2% in Twente.[2] Our patient denied traveling to Twente or other countries, which makes it likely that she got infected in the Groningen area where she resides. The low number of reported cases in comparison to the relatively high seroprevalence suggests that orthohantavirus infections are underdiagnosed, likely due to the subclinical course of the disease or due to misdiagnosis. It is also possible that the infections are mistaken for leptospirosis, since symptoms have many similarities with those of NE. A Dutch study in patients with suspected leptospirosis showed that seven patients had an acute orthohantavirus infection, of which three were initially not diagnosed.[16] This was also the case in our patient, where the orthohantavirus diagnosis was considered only during hospitalisation after a further thorough inquiry. If the rodent exposure had been clarified earlier, a serology test, which is an inexpensive and accessible test, could have been performed and a kidney biopsy could have been avoided.[17]

CONCLUSION

We report a patient with NE due to an infection with the Puumala orthohantavirus acquired in the north of the Netherlands. Reported autochthonous cases are rare, but the high seroprevalence suggests that orthohantavirus infections are underdiagnosed. Orthohantaviruses should be included in the differential diagnosis in patients with flu-like symptoms, renal failure, or thrombocytopenia, also in areas of the Netherlands where orthohantavirus

infections are less common, such as in the north. A thorough exposure inquiry is essential.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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CASE REPORT

An uncommon side effect of thiamazole treatment in Graves' disease

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ABSTRACT

Thionamides (such as thiamazole/methimazole) are a common first line treatment for Graves' disease. Common side effects include rash, urticaria, and arthralgia. However, thionamide treatment has also been associated with a variety of auto-immune syndromes. Here, we describe a patient presenting with mild arthritis after starting thiamazole. Although severe presentation warrants acute withdrawal of the causative agent, our case suggests that milder forms can be successfully treated with anti-inflammatory drugs alone. Recognition of the syndrome is key to warrant timely and effective treatment.

What was known on this topic?

- Rash, urticaria, and arthralgia are the most common side effects of thionamide treatment.
- Thionamide-induced poly-arthritis, as well as more extensive auto-immune syndromes have been described in literature often warranting abrupt cessation of thionamides.

What does this add?

- When thionamide-induced arthritis is recognised timely and in a mild stage, it can be treated with NSAIDs under continuation of the much-desired thionamide treatment.

KEYWORDS

Arthritis, auto-immune, Graves' disease, methimazole, thiamazole, thionamides

INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism, occurring predominantly in women and typically between the age of 20 to 50 years. The disease is caused by thyroid-stimulating immunoglobulins, activating the thyrotropin receptor on the follicular cells of the thyroid gland to secrete and synthesise thyroid hormone. Apart from the typical clinical features for any form of thyrotoxicosis (e.g., hyperactivity, tachycardia, weight loss), Graves' disease may present with distinct signs and symptoms, such as Graves' ophthalmopathy and, less commonly, dermopathy and acropachy (clubbing). In most parts of the world, the first-line treatment for Graves' hyperthyroidism is the lowering of thyroid hormone synthesis by thionamides, such as thiamazole (methimazole), carbimazole, or propylthiouracil (PTU). Common side effects of thionamides include rash, urticaria, and arthralgia. Here, we describe a case of a lesser-known side effect of thionamides.

CASE REPORT

A 41-year-old woman was referred to our outpatient clinic for thyrotoxicosis. She reported agitation, hair loss, change in bowel habits, and fatigue. She had no ophthalmologic complaints and there was no history of recent fever or thyroid pain. Her laboratory results showed thyrotoxicosis with positive thyroid-stimulating immunoglobulins (table 1). A thyroid scintigraphy showed homogeneous uptake of technetium-99m, matching the diagnosis of Graves' disease. We prescribed thiamazole 30 mg once daily and planned to continue with block and replace therapy for the duration of one year.

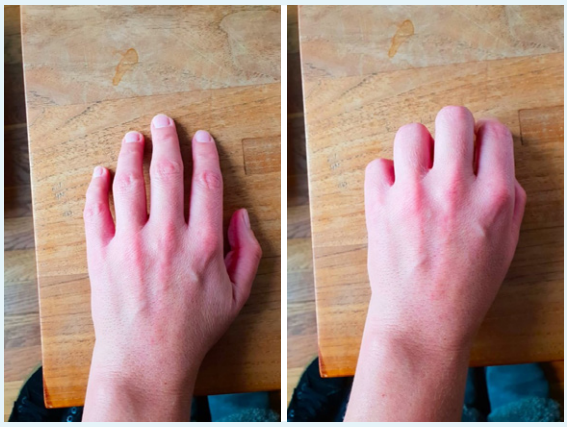
Table 1. *Laboratory values before starting thiamazole and at presentation with arthritis 20 days later.*

	Before thiamazole	20 days later
TSH (U/l)	< 0.02	< 0.02
fT4 (pmol/l)	50.3	15.4
TSI (U/l)	15.3	
CRP (mg/l)		3
ESR (mm/h)		7
Leukocytes (x10^9/l)		5.0
RF		neg
Anti-CCP		neg
HLA-B27		neg

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; fT4 = free thyroxine; HLA = human leukocyte antigen; RF = rheumatoid factor; TSH = thyroid stimulating hormone; TSI = thyroid stimulating immunoglobulins.

Twenty days later, the patient contacted us because of pain and swelling in her hands, right knee, and right ankle. She reported having fever (38.5 °C) a few days previously, but her temperature was now normal. Physical examination revealed arthritis with limited movement of the metacarpophalangeal and proximal interphalangeal joints of the 2nd and 3rd fingers on both hands (figure 1). Although painful, the knee and ankle did not evidently show clinical signs of arthritis. Laboratory evaluation showed normal erythrocyte sedimentation rate, C-reactive protein and leucocyte values, and improving free thyroxine levels (table 1). Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and HLA-B27 were negative. We suspected thiamazole-related arthritis and prescribed naproxen 500 mg two times a day for two weeks, resulting in satisfactory improvement in symptoms to only minor pain in the right knee, without signs of arthritis. After stopping naproxen, she reported minor pain of the hands and right knee for a few weeks, after which the complaints spontaneously disappeared.

Figure 1. *Mild arthritis left hand 20 days after start of thiamazole*



DISCUSSION

Thionamides inhibit the function of thyroid peroxidase, thereby preventing organification of iodine to tyrosine residues and the coupling of iodothyrosines in the thyroid gland. Thionamides can be dosed to completely block thyroid hormone synthesis with addition of levothyroxine substitution therapy (block and replace therapy), or they can be titrated to reduce the amount of thyroid hormone synthesis to satisfactory levels. The most reported side effects of thionamides include rash, urticaria, and arthralgia, mostly well-tolerated and easily treated. Agranulocytosis is a rare but feared complication that can develop abruptly and is a reason to immediately discontinue thionamide-therapy.

Apart from the more common arthralgia, thionamide-treated patients can also present with overt arthritis. The symptoms mostly present as a migratory poly-arthritis, but cases of mono-arthritis or episodic arthritis have also been described.[1-3] A classic presentation consisting of myalgia, poly-arthritis, fever, and rash has been termed antithyroid arthritis syndrome.[4,5] In an observational study in 500 patients with hyperthyroidism receiving either PTU or thiamazole, rheumatic symptoms were observed in 1.6%, only secondary to skin eruptions (1.8%).[4] The symptoms typically present within 2-3 months after initiation of therapy, although arthritis at up to three years has been reported.[3,6,7] As most cases did not present with swelling or erythema, the incidence of overt arthritis is expected to be substantially lower, but still abundantly reported in literature.[3,8,9] Our patient did report a fever at the onset of pain that spontaneously abated after several days. A rash was not observed.

Although causality cannot officially be established in this case study, we have multiple arguments that make a causal relation between thiamazole and arthritis very likely. Both the pattern of poly-arthritis, the fever, and the time-relation with thiamazole matches descriptions in literature.[1-7] An alternative diagnosis seems less plausible, as the patient reported no typical symptoms of a viral (e.g., Epstein-Barr virus, hepatitis B or C, parvovirus B19) cause of the arthritis other than the abated fever. In addition, an auto-immune disease is unlikely, given the normal inflammation markers, the good clinical response to

NSAIDs and the disappearance of symptoms even after cessation of the NSAID therapy.

Thionamide treatment (especially PTU) has been associated not only with arthritis, but with several auto-immune syndromes, including potentially severe anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and drug-induced lupus. Apart from musculoskeletal symptoms, cutaneous lesions and fever, these syndromes can present with renal involvement, serositis, or pulmonary involvement, together with positive auto-antibodies such as anti-nuclear antibodies (ANA) and p-ANCA.[10-12]

The exact mechanism for the development of thionamide-induced auto-immunity is unclear, but several hypotheses have been proposed, such as neutrophil-induced generation of reactive drug metabolites causing auto-immunity in immune compartments;[13] binding of the thiol group of thionamides to macromolecules (such as thyroglobulin), inducing auto-immunity by acting as a hapten;[8] or disturbed regulation of immune function by incorporation of thionamide metabolites in the DNA.[14]

Most literature suggests abrupt cessation of the causative drug after diagnosing thionamide-related arthritis to prevent further auto-immune effects. Switching to an alternative thionamide treatment has been successful in some cases,[2,15] but high rates of cross-reactivity regarding side effects of antithyroid drugs has been demonstrated.[4] Further treatment consists of non-steroidal anti-inflammatory drugs (NSAIDs), usually for one to three weeks. Some authors suggest the use of corticosteroids for more severe or unresolved arthritis, but their efficacy was never established.[7,8] Other than recommended in literature, we chose not to withdraw treatment with thiamazole in our patient, as the arthritis was not extensive and the response to NSAID treatment was satisfactory. After withdrawal of naproxen two weeks later, the patient did report continuous minor pain in the hands and knee, without clinical signs of arthritis, and disappearing spontaneously in a few weeks.

CONCLUSION

In conclusion, thionamide-related arthritis is a relatively uncommon side effect of thionamide treatment, usually presenting with migratory poly-arthritis, but expressing large variations in clinical and laboratory features, with rare cases of drug-induced lupus or ANCA-associated vasculitis. Severe presentation warrants acute withdrawal of the causative agent, but our case suggests that milder forms can be successfully treated with anti-inflammatory agents alone. Recognition of the syndrome is essential for timely and effective treatment.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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PHOTO QUIZ

An impressive chest X-ray...

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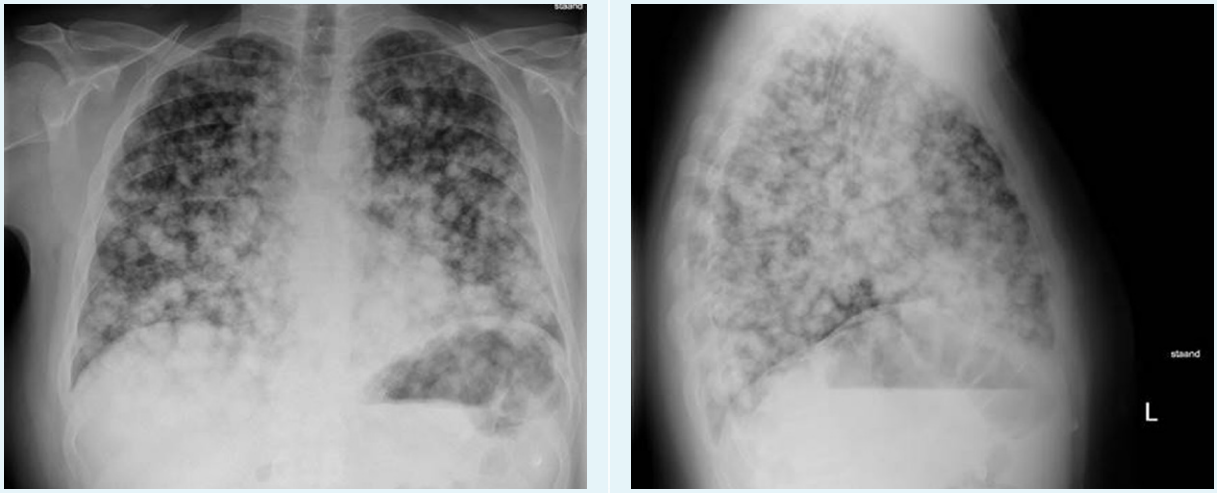
Figure 1. *Chest X-ray; (panel A) PA view and (panel B) lateral view: numerous nodular abnormalities*



A B

PA = posteroanterior

CASE REPORT

A 37-year-old male was referred to the Emergency Department by his general practitioner because of progressive dyspnoea. Medical history was uneventful. He smoked at least 10 cigarettes a day (no e-cigarettes) and did not use drugs. He had not been abroad, had no exposure to animals or chemicals, and delivered papers for a living. A week before presentation, he visited a steam bath in a sauna facility, felt a crack in his upper body and was progressively dyspnoeic since. He only coughed occasionally and did not have a fever, although he experienced heavy perspiration over the last couples of days.

Physical examination showed a sweating and dyspnoeic patient, with a respiration rate 28/minute, $SatO_2$ 94% without supplementary oxygen, heart rate 140/minute, blood pressure 200/140 mmHg and a temperature of 36.7 °C. On auscultation of the lungs, we noticed mild crackles and some inspiratory squawks. Examination of abdomen and extremities was normal. Laboratory results showed an erythrocyte sedimentation rate 100 mm/hour, haemoglobin concentration 8.0 mmol/l, leucocyte count 17.3 x 10^9/l, platelet count 479 x 10^9/l, C-reactive protein 257 mg/l, normal kidney function, normal bilirubin, alkaline phosphatase 155 U/l, gamma glutamyl transferase 168 U/l, aspertate aminotranferase 43 U/l, alanine aminotransferase 16 U/l, and lactodehydrogenase 2523 U/l. The patient refused an arterial puncture for arterial blood gas analysis. EKG showed a sinus tachycardia, without abnormalities.

The chest X-ray (figure 1) surprised and alarmed us.

WHAT IS YOUR DIAGNOSIS?

See page 393 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 392)

AN IMPRESSIVE CHEST X-RAY…

DIAGNOSIS

The first diagnosis that came to mind was malignancy with extensive lung metastases. Differential diagnostic considerations were infection/tuberculosis, toxic-reactive cause, and interstitial lung disease. Because of his age, we asked our patient whether he experienced abnormalities of his testicles (pain, abnormal growth) and asked permission to examine them. He then became reluctant to cooperate in further examination and refused hospital admission. Fortunately, he returned to the hospital the next day, confirming a swollen testicle. Plain CT scan showed an enlarged left testicle of 7.5 cm, retroperitoneal nodular masses in the renal area, and extensive nodular lung metastases (figure 2). Human chorionic gonadotrophin (HCG) measurement showed high levels of 2926 IU/l and alpha-fetoprotein of 14000 ng/ml. This is consistent with stage IIIc poor prognosis non-seminoma testis. He immediately was referred to a tertiary oncology centre and started with intensive chemotherapy consisting of bleomycin, etoposide, and cisplatin. In the first course, bleomycin was omitted considering the massive pulmonary lesions.

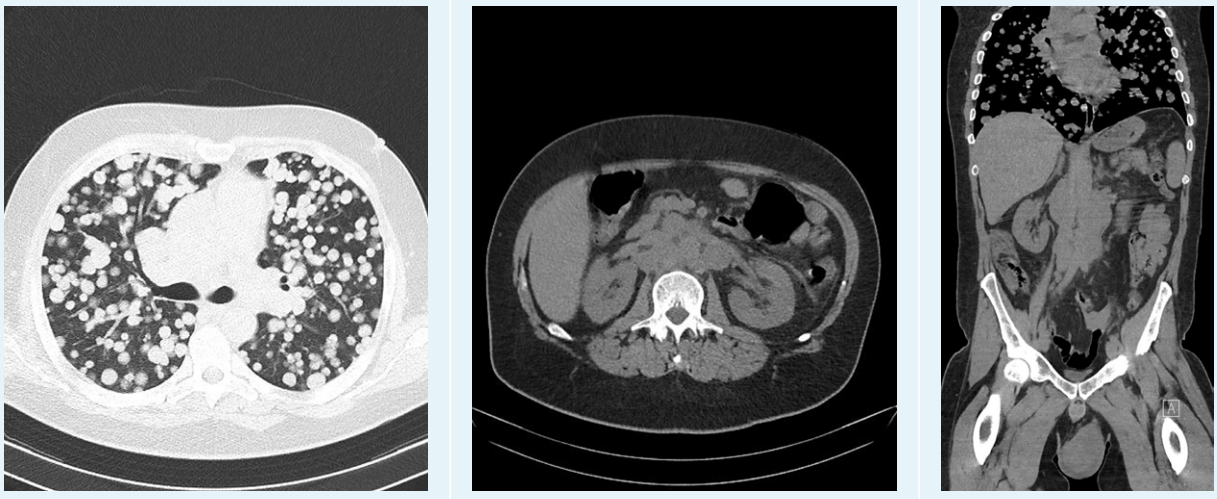
The incidence of testicular cancer is 4-6 per 100,000 men each year, with a slight annual increase. The two types of testicular cancer (seminoma and non-seminoma) are almost equally present. The highest incidence of non-seminoma is seen between 20 to 30 years of age, and of seminoma, between 30 and 40 years of age. Germ cell tumours of the testes are generally fast growing, aggressive tumours. They can spread via lymph vessels to the lymph nodes in the retroperitoneal area at the level of the renal artery and via the venous system to the lungs. Fortunately, these types of malignant tumours have a favourable prognosis. This is mainly the result of intensive chemotherapy regimens and improved surgical techniques.[1]

HCG is a glycoprotein that is primarily produced by trophoblasts of the placenta. Production of HCG is an important feature of germ cell tumours, although it also can be produced by numerous other types of tumours (bladder, lungs, uterus, and pancreas). Nevertheless, in cases with germ cell tumours, HCG can be used for the staging and monitoring of therapy.[2] In general, the first therapeutic step would be an orchiectomy. In this patient, the extensive pulmonary metastases urge for prompt treatment with chemotherapy, prior to an orchiectomy.[3]

DISCLOSURES

The authors have no conflicts of interest to declare.

Figure 2. *(Panel A) plain CT scan of chest (transverse view, lung window) at level of the main bronchus, showing extensive nodular metastases; (panel B) plain CT scan of abdomen (transverse view, at level of renal vessels), showing nodular masses obscuring the contour of the abdominal aorta and the inferior vena cava; (panel C): plain CT PA reconstruction showing an enlarged testicle of 7.5 cm and some hydrocele.*



A B C

PA = posteroanterior

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PHOTO QUIZ

A polyposis syndrome

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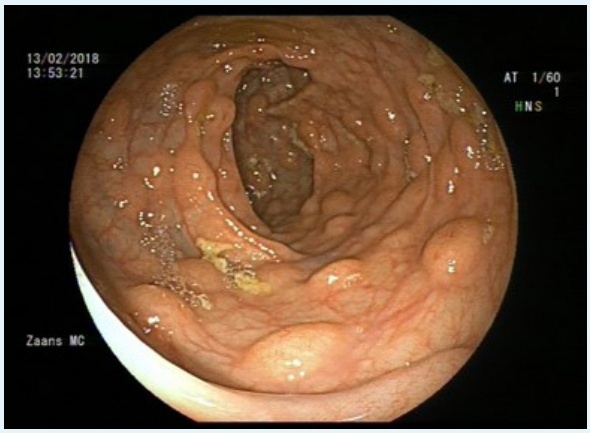
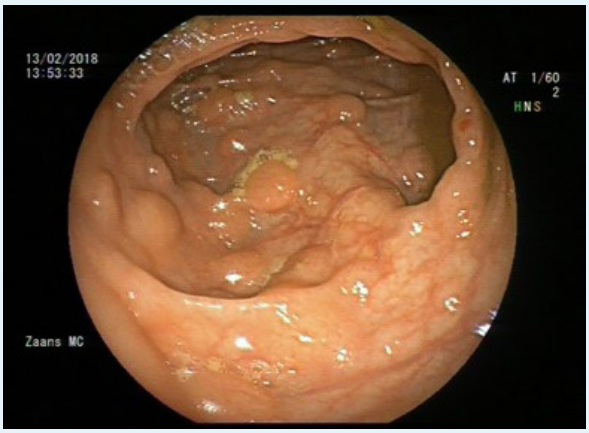
Figures 1A and 1B. *The macroscopic appearance of the colon. Multiple sessile polyps with intact mucosal surface are seen.*



A



B

CASE REPORT

A 49-year-old Caucasian female, with a known irritable bowel syndrome with predominant constipation, presented with a three-month history of progressive diffuse abdominal pain, a bloated belly, and changes in bowel habits including intermittent watery diarrhoea with haematochezia. She had lost 4 kg of weight despite a normal appetite. There was no fever, but she reported night sweats. Laboratory investigation revealed an erythrocyte sedimentation rate of 35 mm (normal value < 20 mm), normal blood count and leucocytes, as well as normal renal and liver function. Investigation of faeces showed infestation with *Dientamoeba fragilis* and a calprotectin of 336 mg/kg (normal value < 50 mg/kg).

Chronic inflammatory bowel disease was suspected. For this reason, a colonoscopy was performed.

The entire colon and rectum showed hundreds of small sessile polyps with intact mucosal surface (Kudo classification type 1) (figures 1A and 1B).

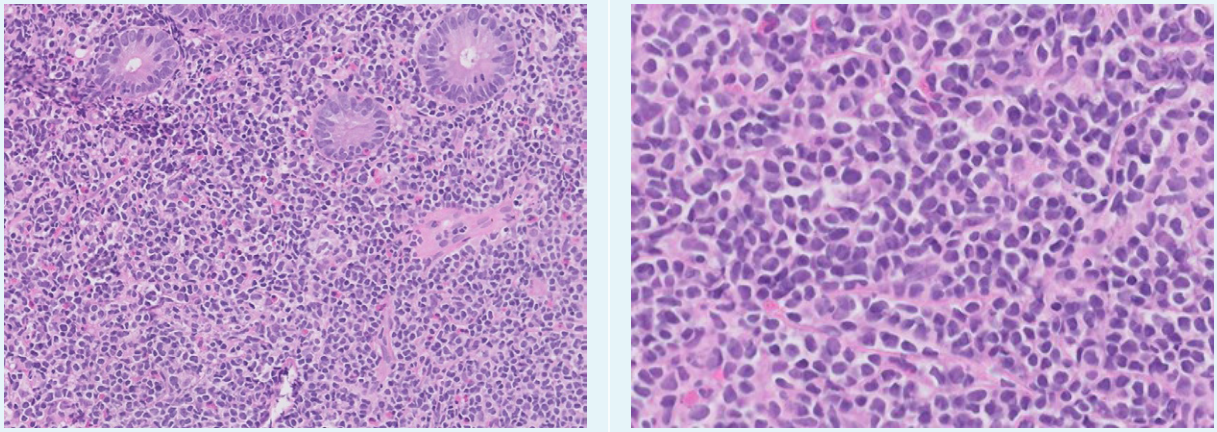
WHAT IS YOUR DIAGNOSIS?

See page 396 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 395)

A POLYPOSIS SYNDROME

Figure 2. *Haematoxylin and eosin (H&E) stain. Panel A: This picture demonstrates a monomorphic population of cells infiltrating between pre-existing glands of colon mucosa. Panel B: The lymphoid cells are small to medium sized and the nuclei shows no nucleoli.*



A B

DIAGNOSIS

Given the macroscopic appearance, a hyperplastic polyposis syndrome was suspected. However, histological examination of biopsy specimens did not confirm the macroscopic diagnosis. A monomorphic lymphoid proliferation with a diffuse architectural effacement in all tissue samples (figures 2A and 2B). Immunostaining revealed mantle cell lymphoma (MCL). Subsequent staging with an FDG-PET/CT scan showed ileocecal and rectal mucosal thickening, mesenterial and retroperitoneal lymphadenopathy, as well as pulmonary nodules, all minimally FDG avid. A CT-guided biopsy of a retroperitoneal lymph node confirmed the diagnosis of MCL. A bone marrow biopsy was positive for MCL (20% infiltration). The MCL International Prognostic Index (MIPI) score was calculated to be 5.5 (low risk).

The patient was treated with alternating cycles of R-CHOP and R-DHAP given every 21 days for a total of six cycles after which, a complete remission was documented by PET/CT scan. Consolidative BEAM chemotherapy supported by an autologous stem cell transplant was given. Subsequently, rituximab maintenance therapy every two months was started. The abdominal complaints disappeared; the stool became normal. A repeat colonoscopy 12 months later showed an entirely normal colon.

MCL comprises about 7% of all non-Hodgkin lymphomas in Western Europe. Involvement of the gastrointestinal tract is reported in 5-20% of all cases. Primary gastrointestinal lymphoma comprises possibly 1-4% of all gastrointestinal malignancies.[1] Localisation in the colon is exceptional. Most patients with multiple lymphomatous polyposis are already known to have MCL.[2] The most common clinical presentation is abdominal pain and weight loss.[3]

MCL most commonly presents in the proximal colon as a mass with ulceration which can lead to intestinal obstruction or intussusception, requiring surgery.[4] Endoscopic features can be heterogeneous, encompassing ulcers, erosions, and polyps, and occasionally presenting as multiple lymphomatous polyposis. The present case shows a MCL diffusely in the colon mimicking a hyperplastic polyposis syndrome.

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PHOTO QUIZ

A fascinating liver abscess

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Figure 1. *CT scan showing liver abscesses in the left liver lobe*

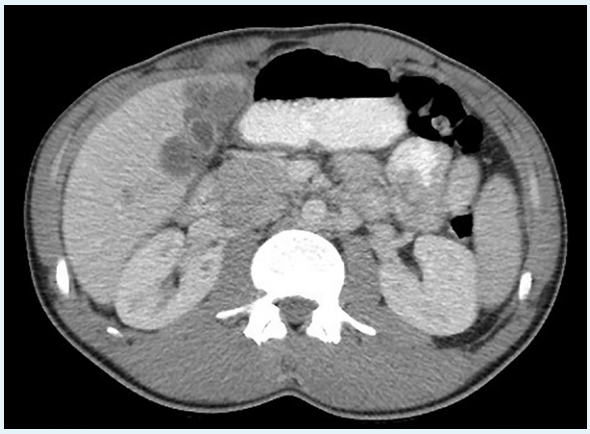
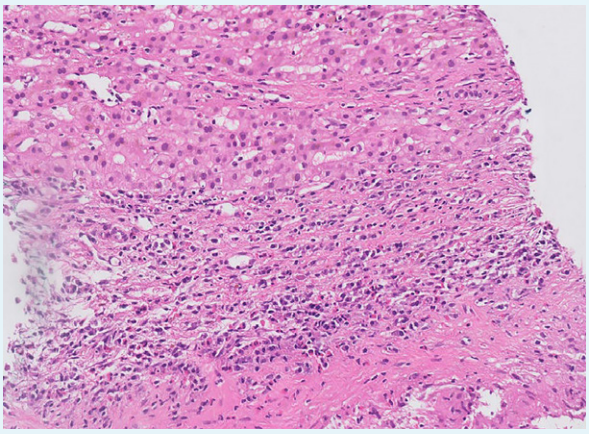


Figure 2. *Histological biopsy of abscess wall in the left liver lobe*



Standard haematoxylin and eosin staining showing connective tissue with eosinophilia, necrosis, and a small amount of liver parenchyma. The necrosis is marked by histiocytes and crystalline structures.

CASE REPORT

A 28-year-old male patient was referred, presenting with a continuously present generalised abdominal pain for two months. He also complained of recurrent fever, night sweats, and weight loss. He had travelled to Bali, Indonesia seven months earlier, where he ate raw vegetables and drank unboiled water. At presentation, he was haemodynamically stabile (blood pressure 134/69 mmHg, heart rate 54 bpm), with a temperature of 37 °C. Physical examination did not reveal any potential diagnostic clues. Laboratory results showed slightly elevated inflammation parameters (erythrocyte sedimentation rate 22mm/h; C-reactive protein 30 mg/l), elevated liver enzymes (ALAT 86 IU/l; ASAT 64 IU/l; gamma-GT 69 IU/l; alkaline phosphatase 209 IU/l; total bilirubin 8 µmol/l), and peripheral eosinophilia (3.1 x 10^9/l). A CT scan of the abdomen demonstrated multiple hypodense structures in the liver suggestive of multilocular abscesses (figure 1). Puncture and histologic biopsy of the abscesses were performed before antibiotics were empirically started. The histological biopsy showed necrotising granulomatous inflammation with eosinophilia (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 398 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 397)

A FASCINATING LIVER ABSCESS

DIAGNOSIS

Bacterial culturing of the punctate remained negative. Due to the peripheral eosinophilia, a parasitic infection was suspected. Serology of *Entamoeba histolytica*, schistosomiasis, toxocariasis, echinococcosis, and strongyloides were negative. However, *Fasciola hepatica* serology was markedly positive (indirect haemagglutination titre 1:20480 [reference range < 160]). A single oral dose of triclabendazole 10 mg/kg was given, after which, his complaints resided, laboratory results normalized, and the abscesses resolved.

Fascioliasis is a food-born trematode liver fluke infection caused by *Fasciola hepatica* and *Fasciola gigantica*. It is an increasing public health problem[1] and classified as a neglected tropical disease.[2] *Fasciola hepatica* is endemic to Asia, Oceania, the Americas, and Europe.[3] Ruminants such as sheep and cattle are the common hosts. Humans are incidental hosts who acquire the infection by the ingestion of contaminated freshwater plants or water.[2] The life cycle of *Fasciola hepatica* begins with adult flukes releasing their eggs in the biliary ducts of their host.[4] These eggs are passed in the stool and embryonated in water, releasing miracidia who subsequently invade snails. Miracidia develop into cercariae which leave the snails and encyst (metacercariae) on freshwater plants. Metacercariae are then ingested by definitive hosts, excyst in the duodenum and migrate through the peritoneal cavity and liver parenchyma into the biliary ducts, where they develop into adult flukes. Clinically, fascioliasis can present during the acute (i.e., liver) or chronic (i.e., biliary) phase. The acute phase starts approximately two to three months after ingestion and is caused by metacercariae migrating through the liver. Patients present with fever and abdominal pain, sometimes accompanied by anorexia, nausea, vomiting, myalgia, coughing, or urticaria. The chronic phase, after approximately six months, is usually asymptomatic, but can also manifest with biliary colic, cholangitis, jaundice, or pancreatitis due to biliary tract obstruction. Treatment with one dose of triclabendazole, taken with a fatty meal, is a very effective cure. However, as this drug is only registered for veterinary use in the Netherlands, it may be hard to obtain. The present case shows that fascioliasis can present with liver abscesses and that peripheral eosinophilia forms a potential diagnostic clue.

CONCLUSION

Fascioliasis can present as liver abscesses.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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PHOTO QUIZ

A bone disorder with skin lesions

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Figure 1. *Skin lesions of both hands and feet*

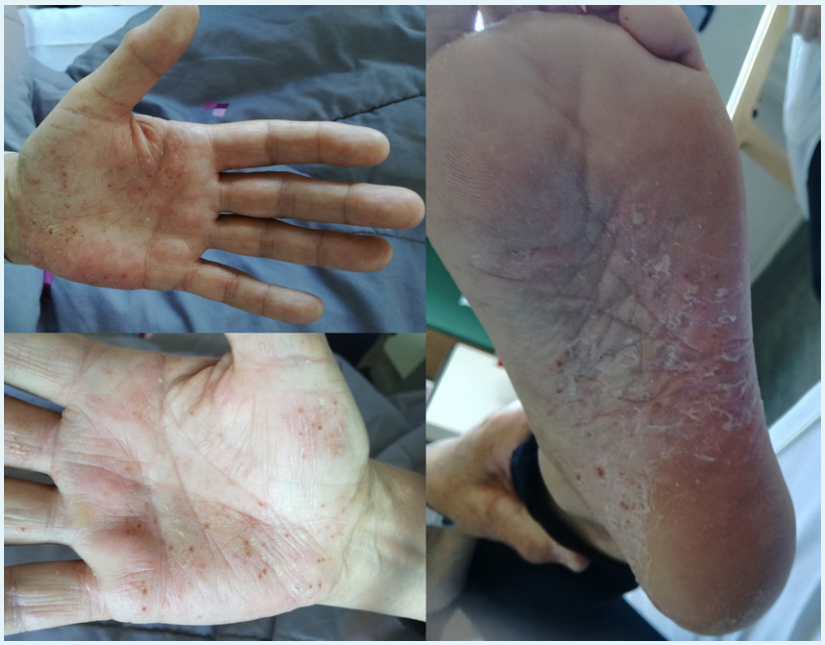
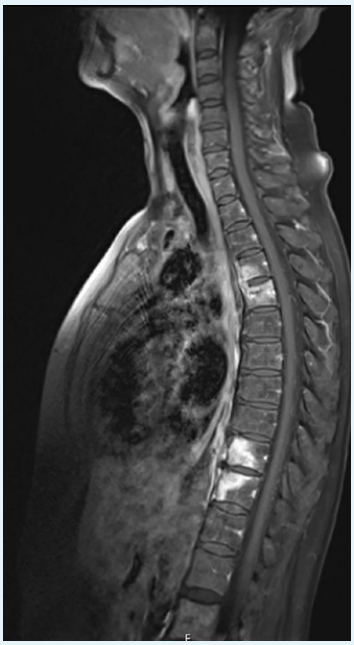


Figure 2. *MRI of the thoracic spine: inflammation at Th4-Th5 and Th10-Th11*



CASE REPORT

A 61-year-old female, being analysed by a neurologist for back pain, was referred to internal medicine because of an abnormality in the MRI of her spine. The patient was admitted to the hospital with severe pain of the upper back which started four months ago. In addition to this pain, she often experienced sternoclavicular pain and swelling, for which, she took ibuprofen daily. She did not have a fever or any other complaints. Her medical history showed seronegative rheumatoid arthritis of metacarpophalangeal and proximal interphalangeal joints in 2011, for which she was treated with methotrexate and hydroxychloroquine until 2012. She was asymptomatic for years without medication.

Physical exam revealed acneiform skin lesions of both hands and feet as shown in figure 1, for which, she used topical clobetasol prescribed by a dermatologist. Laboratory investigations did not reveal any abnormalities with C-reactive protein < 4 mg/l, erythrocyte sedimentation rate 5 mm/h and normal haemoglobin, platelets, leukocytes, kidney function, and liver enzymes. An MRI showed inflammation at Th4-Th5 and Th10-Th11 (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 400 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 399)

A BONE DISORDER WITH SKIN LESIONS

DIAGNOSIS

At first, the MRI appeared to show spondylodiscitis. For this reason, the patient was referred to internal medicine. However, this diagnosis seemed unlikely because there were no clinical signs of infection and although the MRI did show paravertebral oedema, the disc seemed unaffected.

Based on the combination of vertebral osteitis and pustulosis palmaris on both hands and feet, and a previous episode of sternoclavicular pain and swelling, we suspected synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. SAPHO syndrome is a rare inflammatory syndrome of bone, joints, and skin with the above-mentioned characteristics.

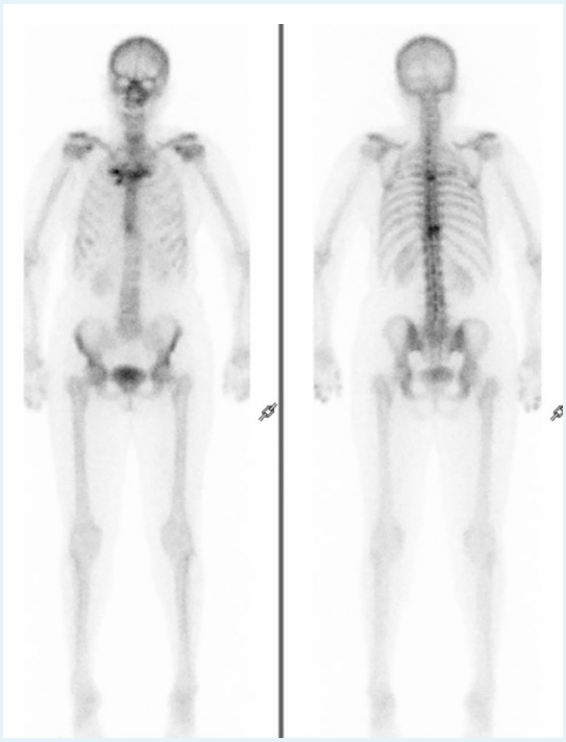
The pathogenesis of the syndrome is still unclear. Aetiology is most likely multifactorial with genetic factors as well as infectious and immunological complements contributing to the disease.[1,2] There are no validated diagnostic criteria for SAPHO syndrome. Diagnosis is based on the patient's history with characteristic combinations of features and typical radiological findings.[2] Other explanations like infection, malignancy, or classic rheumatic diseases should be excluded.

To confirm the diagnosis in this patient, we performed an additional bone scintigraphy showing a so-called 'bull's head' change caused by sternoclavicular hyperostosis, characteristic for SAPHO syndrome with sternoclavicular involvement (figure 3).[1] The diagnosis SAPHO syndrome was made.

Treatment is recommended for all patients to ease symptoms and prevent complications. Initial therapy consists of nonsteroidal anti-inflammatory drugs. Second-line treatment may include a tumour necrosis factor (TNF) inhibitor, methotrexate, bisphosphonates, or anti-interleukin-1 therapy.[2,3] There is little evidence for choice of second-line treatment and recommendations are mostly based on case series. Although treatment can be difficult, long-term prognosis is good if promptly diagnosed and treated.[3]

After starting naproxen (500 mg, 2 times daily), the patient's symptoms improved and she was discharged.

Figure 3. *Bone scintigraphy: sternoclavicular hyperostosis with sternoclavicular involvement and inflammation at Th4 and Th10*



During follow-up, the patient developed peripheral arthritis, also commonly seen in SAPHO syndrome. Due to progression of her disease, she started treatment with additional methotrexate. Because of side effects of methotrexate, she is now starting a TNF inhibitor adalimumab.

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CASE REPORT

Hypokalaemia and peripheral oedema in a Cushingoid patient with metastatic prostate cancer

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ABSTRACT

We report on a 75-year-old man with a history of metastatic prostate cancer who presented with haematuria, peripheral oedema, metabolic alkalosis, hypokalaemia, and hypertension. Laboratory evaluation was compatible with the diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome and suggestive of ectopic ACTH production. Pathology of a prostate biopsy specimen showed a large cell neuroendocrine carcinoma (LCNEC) of the prostate. This report describes a case of Cushing's syndrome that was probably caused by ectopic ACTH secretion by a LCNEC of the prostate.

What was known about this topic?
Cushing's syndrome is a known paraneoplastic syndrome often caused by neuroendocrine tumours.

What does this add?
Neuroendocrine differentiation in prostate cancer patients is likely to be underreported. It should be considered more often in patients with rapid clinical deterioration.

KEYWORDS

Cushing's syndrome, ectopic ACTH production, large cell neuroendocrine carcinoma, prostate cancer

INTRODUCTION

Adenocarcinoma of the prostate is the most frequent malignancy diagnosed in men. In metastatic disease, blocking androgen synthesis and/or the androgen receptor is the cornerstone treatment modality. Ultimately, all patients with metastatic prostate cancer (PC) will develop resistance with a fatal outcome. In late-stage metastatic prostate cancer, typically in the setting of aggressive visceral metastases, clinical manifestations attributed to neuroendocrine tumour dedifferentiation can become apparent.

CASE REPORT

A 75-year-old man with a two-year history of metastatic prostate cancer was admitted to the hospital due to macroscopic haematuria. He had indistinct complaints of muscle weakness and emotional lability. His hormone-sensitive prostate cancer (HSPC) had been treated with upfront docetaxel in combination with a luteinising hormone releasing hormone agonist, but after one year, the disease was considered castrate-resistant prostate cancer (CRPC) and treated with enzalutamide. Physical examination revealed a blood pressure of 183/83 mmHg, a mild dorsocervical fat pad, and bilateral pitting oedema. There was no hyperpigmentation, moon facies, or abdominal striae. Initial laboratory examination revealed a hypokalaemia of 2.7 mmol/l (3.5-5.0 mmol/l), a metabolic alkalosis, a prostate-specific antigen (PSA) of 90ug/l (< 4.0 µg/l), and lactate dehydrogenase (LDH) 909 U/l (< 248 U/l). Additional tests showed a midnight cortisol in saliva (340 nmol/l; N < 4 nmol/l), 24-hour urinary free cortisol (UFC)

16,000 nmol/24 h (15-130 nmol/24 h), serum cortisol 1.750 nmol/l (130-540 nmol/l), and ACTH 40.4 pmol/l (1.60-13.9 pmol/l). Cortisol was not suppressed (1.553 nmol/l) after a low dose of dexamethasone (1 mg) overnight. Abdominal CT scan demonstrated stable para-aortal lymphadenopathy and bone metastases, but a progressive tumour of the prostate and bilateral enlarged adrenal glands. An MRI scan of the pituitary did not reveal any abnormalities. Pathology of the prostate biopsies showed a large cell neuroendocrine carcinoma (LCNEC) of the prostate (figure 1). Immunohistochemical staining of the prostate biopsy showed tumour cells positive for CD56, chromogranin, and synaptophysin, but staining for ACTH was negative. An additional PET scan with Ga-68-Edotreotide (DOTATOC) showed increased expression of somatostatin receptors in a subset of the bone metastases and part of the prostate.

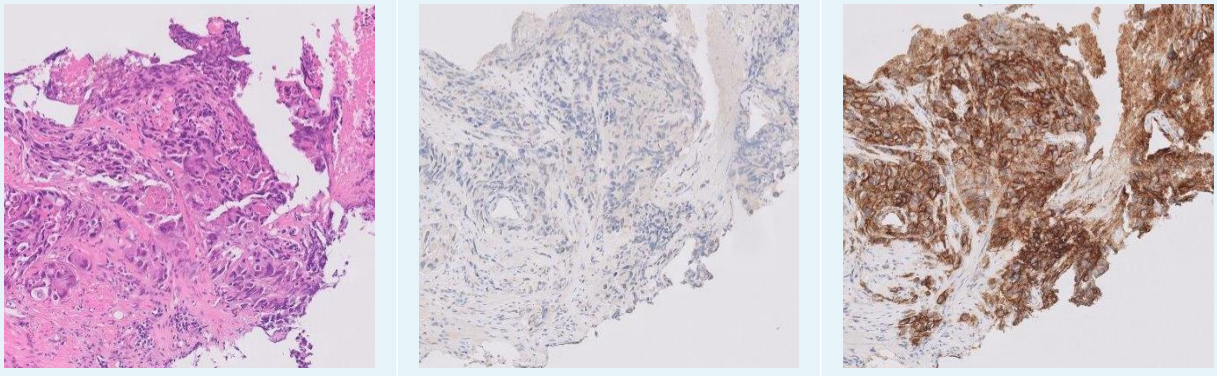
The diagnosis of Cushing's syndrome was made, most probably due to ectopic production of ACTH by a metastatic LCNEC of the prostate. The patient was treated symptomatically with potassium chloride and potassium-sparing diuretics (spironolactone), in combination with ketoconazole, a cortisol synthesis blocking agent. Urinary cortisol excretion was monitored to evaluate the efficacy of this treatment. After five days of ketoconazole 400 mg twice daily, 24-hour urinary free cortisol excretion declined to 3.500 nmol/24 h. We decided not to perform additional invasive testing, bilateral adrenal extirpation, or to initiate palliative chemotherapy as the medical condition of the patient deteriorated. The patient died within several weeks after diagnosis.

DICUSSION AND CONCLUSION

ACTH-dependent Cushing's syndrome is caused by ectopic ACTH secretion in approximately 10-15% of cases. It has been associated with a wide variety of tumours, usually carcinomas. Ectopic secretion is most frequent diagnosed in pulmonary small cell cancer but also occurs in other, often malignant neuroendocrine tumours.[1-2] A small cell neuroendocrine tumour of the prostate has been reported in 1-3% of cases as the cause for Cushing's syndrome.[3] To the best of our knowledge, Cushing's syndrome caused by ectopic ACTH secretion by a LCNEC of the prostate has not been reported in the literature to date.

The lack of abnormalities on an MRI scan of the pituitary decrease the likelihood that an ACTH-producing pituitary microadenoma was the source of the ACTH hypersecretion, although it is important to note that a negative pituitary MRI in itself cannot exclude Cushing's disease. The timeline of the clinical symptomatology of Cushing's syndrome in our patient is also suggestive of a relationship with the patient's prostate cancer since symptoms only recently occurred and coincided with the clinical progression of the metastatic disease. Furthermore, the negative immunohistochemical ACTH staining does not exclude an ectopic ACTH-secreting tumour as it has been reported that tumour immunostaining for ACTH can be negative in up to 30% of ACTH-secreting tumors.[2] Neuroendocrine cells, which lack androgen receptors, are a part of the normal prostate tissue, where they play a regulatory role in proliferation and secretion of the prostate epithelium.[4-5] In vitro experiments have shown that during androgen deprivation treatment (ADT), prostate

Figure 1. *A: Prostate biopsy showing atypical epithelial cells with enlarged nuclei; B: PSA staining negative; C: Immunohistochemical staining synaptophysin, marker of NE differentiation.*



A B C

NE = neuroendocrine; PSA = prostate-specific antigen

adenocarcinoma cells have the capacity to transdifferentiate to a more neuroendocrine (NE) phenotype, a process called NE transdifferentiation. Restoring the androgens can suppress this process.[6-7] Clinically, a substantial proportion of pre-treated end-stage prostate cancer patients show salient features of *de novo* small neuroendocrine cell carcinomas, mostly with an aggressive behaviour, and often with visceral metastases. Although most patients are not routinely biopsied in end-stage disease, it has been estimated that at least 25% of the patients with advanced prostate cancer will develop neuroendocrine prostate cancer.[8]

LCNEC of the prostate is extremely rare as indicated by a recent systematic review and pooled analysis of 20 patients.[9] In most patients, the LCNEC of the prostate occurred after long-standing androgen deprivation in the setting of prostate cancer. The clinical manifestations were aspecific and most cases, like our patient, were diagnosed at the time of palliative transurethral resection of the prostate for urinary symptoms. Ectopic hormonal production was not reported. Prognosis is poor, and although systemic chemotherapy may have some benefit, most patients die within a few months.[9]

The symptomatic treatment of ectopic Cushing's syndrome includes potassium suppletion, potassium sparing diuretics, cortisol synthesis blocking agents (e.g., ketoconazole, metyropone, etomidate), and bilateral adrenal extirpation. As is illustrated by our case, ketoconazole monotherapy is unlikely to suffice and addition of other cortisol blocking agents or even bilateral adrenalectomy should be considered. After a full biochemical control, palliative chemotherapy can be considered in order to achieve tumour shrinkage and thereby decrease ectopic ACTH production.

LCNEC of the prostate is extremely rare and mostly occurs after long-term hormonal therapy of prostatic adenocarcinoma. NE differentiation during ADT should be suspected in all prostate cancer patients with rapid clinical deterioration.

DISCLOSURES

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LETTER

A diagnostic tool for self-poisoned patients: Analysis of gastric content and lavage fluids

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ABSTRACT

Approximately 500 patients per year are admitted to the emergency department (ED) of the Erasmus University Medical Center presenting with intoxications with medication. For adequate treatment, it is sometimes important to know which drugs in which quantities were ingested. This can require laboratory analysis of blood or urine samples; however, these samples do not provide information about the possible effects that can still be expected.

We performed toxicological screening on the gastric content of three patients admitted to our ED in January and February 2018. These patients underwent gastric lavage or received a gastric tube as part of routine care. The gastric fluid was analysed via UPLC-MS/MS using the Waters method for toxicological screening.

In all three patients, we successfully determined drugs in the gastric content. In two patients, we identified more different drugs in the gastric content than in blood plasma. In the other patient, admitted approximately six hours after a severe autointoxication with the betablocker metoprolol, we found significant amounts of metoprolol in the gastric content acquired by gastric lavage. We therefore believe that analysis of gastric content after an intoxication can have multiple applications; for example, it may provide information about symptoms of intoxication that can be expected, it may aid patient care and may provide insight in the toxicokinetics of different drugs.

In conclusion, we demonstrate that toxicological screening and quantification of drug levels in gastric content is possible and has potential as an adjunct in patient care, but limitations need to be addressed before implementation in clinical practice.

INTRODUCTION

Self-poisoned patients are a high burden for emergency departments (EDs)[1-6] and intensive care units (ICUs).[6-8] Self-poisoned patients are often considered unreliable, as they can either under- or overestimate the amount of medications taken. Patients history can be difficult due to a lowered consciousness[9] or amnesia, as a result of the intoxication.[10] In addition to toxidromes and clinical features,[11] clinicians therefore often use qualitative and quantitative drug analysis in blood and urine.

Laboratory analysis can be helpful in the management of a self-poisoned patient, as it may provide additional clues.[12] Previous research has shown that in 18% of cases of self-poisoning, clinically important differences were found between information available at admittance and information gained with analysis of body fluids.[13] Various analytical techniques might be available in the laboratory. Each analytical method however, has its own benefits and limitations, that vary from duration of the analysis to the specificity of the method and may therefore be a challenge in patient care.[14] Another challenge is that it is not always possible to obtain usable patient material (e.g., blood or urine) from an intoxicated patient. The care for intoxicated patients may therefore benefit from analytical methods for the determination of drugs in alternative matrices.

In this letter, we describe how we performed analysis of gastric content acquired by either aspiration or gastric lavage. We describe how this method, in our opinion, has the potential to aid patient care and how it can possibly provide insight in toxicokinetics, and how it may improve the effectiveness of certain interventions, such as gastric lavage.

SETTING

The Erasmus University Medical Center (Rotterdam, the Netherlands) is a tertiary hospital with approximately 30,000 ED visits a year. In approximately 500 patients suspected for (severe) intoxication, toxicological analysis is performed. The laboratory of the hospital pharmacy has various analytical methods for blood and urine samples, which are validated according to the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. No validated method for toxicological screening of gastric content is available.

The duration of analysis differs between methods. On average, including time for sample preparation, analysis of a sample via autoanalyzer requires approximately 30 minutes. Dedicated methods for one drug or one group of drugs requires approximately one hour. Toxicological screening via Ultra performance liquid chromatography - tandem mass spectrometer (UPLC-MS/MS) (regardless of sample type), including sample preparation, requires approximately two hours.

Samples of gastric content were collected from three patients admitted to the ED, in whom gastric lavage was performed as part of routine patient care. Samples were thoroughly mixed to ensure that all compounds were dissolved and were then prepared for analysis in the same manner as the validated blood sample preparation. Then samples were analysed via toxicological screening (UPLC-MS/MS, Waters).

RESULTS

The first patient was a male who was found unconscious (Glasgow Coma Scale E1M1V1) next to an empty bottle of hard liquor and blister packs accounting for a maximum of 60 tablets of tramadol 50 mg. Clinical presentation was in accordance with a hypnotic/sedative toxidrome. The patient was intubated and his stomach was pumped. Results of the different analysis performed can be found in table 1.

Table 1. *Analyses and results of the first patient*

Method of analysis	Type of sample	Compounds
Autoanalyzer	Blood plasma	Ethanol (4.9 ‰)
UPLC-MS/MS	Blood plasma	Tramadol
UPLC-MS/MS	Gastric content	Tramadol, lidocaine, cotinine, and nicotine

UPLC-MS/MS = Ultra performance liquid chromatography - tandem mass spectrometer

The second patient was a male who presented at the ED after a suicide attempt with approximately 40 tablets of lormetazepam 2 mg and approximately 40 tablets with prolonged release of metoprolol 50 mg. His prescribed medication also included paroxetine and quetiapine. He was treated with glucagon and high-dose insulin and glucose. Gastric lavage was performed approximately six hours after ingestion, because of the potential severity of the intoxication and the ingestion of prolonged release tablets. This resulted in 3.75 litres of lavage fluid. Metoprolol was then quantified via UPLC-MS/MS (Thermo). The sample had to be diluted 100 times since the concentration outreached the upper limit of quantification. Metoprolol concentration in the diluted sample was 575 µg/l and thus 57500 µg/l or 57.5 mg/l in the undiluted sample. Since the sample was taken from 3.75 litres of homogenous lavage fluid, approximately 200 mg of metoprolol (approximately 10% of the estimated ingested tablets) was present in the lavage fluid. Table 2 shows the results of all performed analyses in this patient.

The third patient was a female who was intubated prehospital by a mobile medical team because of a lowered consciousness (Glasgow Coma Scale E1M1V1). There was a high suspicion of an intoxication with clomipramine

Table 2. *Analyses and results of second patient*

Method of analysis	Type of sample	Compounds identified
UPLC-MS/MS	Blood plasma	Metoprolol (97 µg/l, therapeutic)
UPLC-MS/MS	Gastric content	Metoprolol (approx. 200 mg/3.75 l lavage fluid), quetiapine, lidocaine, paroxetine, benzodiazepines

UPLC-MS/MS = Ultra performance liquid chromatography - tandem mass spectrometer

Table 3. *Analyses and results of third patient*

Method of analysis	Type of sample	Compounds identified
Autoanalyzer	Blood plasma	Paracetamol (2 mg/l; subtherapeutic)
UPLC-MS/MS	Blood	Quetiapine, lorazepam, lidocaine, clomipramine (22 µg/l), paracetamol
UPLC-MS/MS	Gastric content	Lorazepam, lidocaine, clomipramine, imipramine, chlorpromazine, paracetamol, caffeine, and theophylline

UPLC-MS/MS = Ultra performance liquid chromatography - tandem mass spectrometer

and lipid emulsion therapy was initiated in the prehospital setting. In the ED, gastric lavage was performed. Table 3 shows the results of the different analyses.

INTERPRETATION

In this manuscript, we describe three self-poisoned patients with potentially severe intoxications, in whom we performed analyses on gastric content.

In patient 1, we found tramadol in the blood and tramadol, cotinine, nicotine, and lidocaine in the gastric content. This demonstrates the possibility of detecting toxins in gastric content with toxicological screening via UPLC-MS/MS. We believe that lidocaine – used during the intubation to lubricate the tube - was present in the gastric content only because it is metabolised rapidly after absorption and thus not detectable in the blood. This also indicates that it is possible to detect toxins that are not yet (fully) absorbed in the gastric content, and that this analysis can therefore provide information about the type and severity of the intoxication that can be expected.

In patient 2, we identified metoprolol in both the blood and gastric content, even six hours after ingestion. We also could quantify the metoprolol level in the gastric lavage fluid. This shows that gastric analysis can be used to provide new insights into the effectiveness of gastric lavage and may also be used as a tool in research. Furthermore, although the patient's story was deemed reliable in this case, we determined that the patient had also ingested quetiapine and paroxetine, which were unreported by the patient. This illustrates that analysis of gastric content can help verify a patient's story and perhaps fill in missing information that can better inform the course of treatment.

In patient 3, we confirmed the findings of patients 1 and 2. We found more toxins in gastric content than in blood. Due to lipid therapy, the patient's blood was lipaemic; lipophilic drugs that were present may have high affinity for the lipid phase. When blood plasma samples are prepared, these drugs may precipitate and therefore not be measured in the analysis. Gastric content is not affected by lipid therapy and may provide additional information when analysis of blood samples is impractical (e.g., in lipaemic samples).

Analysis of gastric content in the intoxicated patient is not new and has been previously described in literature.[15-19] This research was conducted before 1980 and since then, methods of analysis have improved. Recently, the analysis of gastric contents spiked with different toxins collected in non-intoxicated patients by ambient-mass-spectrometry was described.[20] Analysis of gastric content is also used in other fields such as forensic toxicology.[21,22] However, gastric analysis in an acute intoxication is not regularly performed. We illustrate that this can provide useful information.

Introduction of this method into clinical practice is only possible when certain issues are resolved. Firstly, the used method for toxicological screening should be validated for analysis of gastric content. Adequate sample preparation and influence of the use of gastric content on the results and the UPLC-MS/MS should be part of this validation. Secondly, analysis of gastric content can at this moment, only be used in patients that either undergo gastric lavage or have an orogastric or nasogastric tube. In current practice, gastric lavage is performed in only a small percentage of patients as indications are limited. Patients with a gastric tube are seen more frequently, for example, patients who are intubated. Gastric contents can easily be acquired in these patients, but it will only provide qualitative results. Lastly, toxicological screening via UPLC-MS/MS, both in blood plasma and gastric content, requires more time than other available methods. Therefore, this method will have the most added value in intoxications with unknown substances. For intoxications with known substances, the use of other methods will be faster and thus more suitable.

In conclusion, we demonstrate that toxicological screening of gastric content has potential as an adjunct in patient care. Our results are promising, but future research is required to standardise and validate methods on obtaining, preparing, and analysing samples and other cautions should be considered before this method can be introduced into clinical practice.

DISCLOSURES

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The final post?

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