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Time trend analysis of long term outcome of patients with haematological malignancies admitted at dutch intensive care units

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Summary

A few decades ago, the chances of survival for patients with a haematological malignancy needing Intensive Care Unit (ICU) support were minimal. As a consequence, ICU admission policy was cautious. We hypothesized that the long-term outcome of patients with a haematological malignancy admitted to the ICU has improved in recent years. Furthermore, our objective was to evaluate the predictive value of the Acute Physiology and Chronic Health Evaluation (APACHE) II score. A total of 1095 patients from 5 Dutch university hospitals were included from 2003 until 2015. We studied the prevalence of patients' characteristics over time. By using annual odds ratios, we analysed which patients' characteristics could have had influenced possible trends in time. A approximated mortality rate was compared with the ICU mortality rate, to study the predictive value of the APACHE II score. Overall one-year mortality was 62%. The annual decrease in one-year mortality was 7%, whereas the APACHE II score increased over time. Decreased mortality rates were particularly observed in high-risk patients (acute myeloid leukaemia, old age, low platelet count, bleeding as admission reason and need for mechanical ventilation within 24 h of ICU admission). Furthermore, the APACHE II score overestimates mortality in this patient category.

Keywords: haematological malignancies, prognostic, clinical studies, statistics, oncology.

Up to 15% of patients with a haematological malignancy require admission to an Intensive Care Unit (ICU) in the early phases of their disease (Schellongowski *et al*, 2011; Bird *et al*, 2012; Azoulay *et al*, 2013; van Beers *et al*, 2016). These patients are immunocompromised due to disease- and therapy-related bone marrow dysfunction and immunosuppressive treatment, and are therefore at risk for infections. Patients with a haematological malignancy are more critically ill and have higher hospital mortality rates compared to other cancer patients and ICU patients in general (Taccone *et al*, 2009).

Two decades ago, the chances of survival for this patient category were minimal; ICU mortality rates were over 50% and hospital mortality was reported to be up to 80% (Lloyd-Thomas *et al*, 1988; Groeger *et al*, 1998; Wright *et al*, 2003).

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Therefore, haematologists and intensivists were reluctant to admit patients with a haematological malignancy to the ICU, in particular following allogeneic stem cell transplantation, after which the one-year mortality rate was reported to be over 80% (Townsend *et al*, 2013; Platon *et al*, 2016).

However, survival rates of haematological patients admitted to the ICU seem to have improved in recent years; reported ICU survival ranges from 46% to 66% (Vandijck *et al*, 2008; Azoulay *et al*, 2013; Oeyen *et al*, 2013; van Vliet *et al*, 2014). Although this is encouraging, some studies still report that less than half of the patients admitted to the ICU survive (Grgić Medić *et al*, 2015). Postulated reasons for improved outcome are better haematological care, including new targeted drugs for treating haematological malignancies and improved supportive care (Major *et al*, 2001; Brenner, 2002; Walsh *et al*, 2004). In general, the chance of cure for haematological malignancy seems to be growing (Gondos *et al*, 2008; Sant *et al*, 2014). Overall ICU mortality rates also seem to be decreasing (Zimmerman *et al*, 2013), but it is unclear if the cause for better outcomes of this specific patient group is due to better haematological treatment options, better ICU care, or to an even more selective ICU admission policy. If the latter is true, improved outcome may be due to a more restrictive admission policy in which the most critically ill patients are not admitted to the ICU. As most studies with an improved outcome have focused on short-term survival (Thiery *et al*, 2005; Hampshire *et al*, 2009; Taccone *et al*, 2009; van Vliet *et al*, 2014; Grgić Medić *et al*, 2015), it is unclear whether long term outcome of patients with a haematological malignancy is actually improving.

With use of a large multi-centre database that holds information for the last 13 years, we aimed to provide evidence of improved long-term outcome of patients with a haematological malignancy admitted to the ICU and whether any effect is influenced by a restrictive admission policy or not. Furthermore, our objective was to evaluate the predictive value of the Acute Physiology and Chronic Health Evaluation (APACHE) II score, a severity-of-disease classification system where higher scores correspond to a higher risk of death, for patients with a haematological malignancy admitted to the ICU, because the use of the APACHE score in these patients may be inaccurate (Benoit *et al*, 2003; Bird *et al*, 2012; Sawicka *et al*, 2014).

Methods

Data collection

We performed a multi-centre retrospective observational study between January 2003 and August 2015. The prospectively collected dataset of the Dutch National Intensive Care Evaluation (NICE) registry and the DBC Healthcare Cost and Utilization databases of five University Hospitals in the Netherlands (Academic Medical Centre Amsterdam, Erasmus Medical Centre, Leiden University Medical Centre, Radboud University Medical Centre Nijmegen and the University Medical Centre Groningen) were merged. Missing information was completed with use of the electronic patient records. All ICUs were close format ICUs and daily multidisciplinary meetings with the haematologists and intensivists were common in each hospital.

Only patients with a proven haematological malignancy that were admitted at an ICU with an acute admission reason were included in our study. Ethical approval was obtained on 23 August 2016 from the Medical Ethics Committee of the University Medical Centre Groningen (METc 2016·396.). Patients admitted after elective surgery or for a diagnostic procedure, e.g. bronchoscopy, were excluded. Only first ICU admissions were taken into account. To further exclude non-acute reasons for ICU admission we excluded all patients who were discharged alive within 24 h after ICU admission.

Baseline characteristics included age; gender; malignancy type; disease status at the time of admission; need for mechanical ventilation; vasoactive medication; reason of admission; previous stem cell transplantation; renal replacement therapy; presence of infection and length of stay at the ICU. Laboratory variables included bilirubin level, creatinine level, neutrophil and platelet counts. Severity of illness in the first 24 h of ICU admission was assessed using the APACHE II score (Knaus *et al*, 1985). All patients had at least one year follow-up for survival.

Definitions

Haematological malignancies were categorized into seven groups: acute lymphocytic leukaemia (ALL); acute myeloid leukaemia (AML); chronic lymphocytic leukaemia (CLL); chronic myeloid leukaemia (CML); Hodgkin lymphoma (HL); non-Hodgkin lymphoma (NHL) and multiple myeloma. Disease status was defined as active disease or complete remission. Patients had active disease when there was no complete remission or a relapse. The use of stem cell transplantation, if present, was classified as autologous or allogeneic transplantation.

Patients were categorized based on their reason of admission: disease-related; sepsis; anaphylactic shock; intestinal perforation; pulmonary embolus; neurology; bleeding; toxicity treatment- or other.

The APACHE II score was used as the main indicator of illness severity in the first 24 h of ICU admission. The APACHE II score is a severity-of-disease classification system; it is one of several ICU scoring systems. The score is applied within 24 h of ICU admission. An integral score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. We used the APACHE II score because the APACHE IV score was not complete for the first period of our cohort. Other factors associated with severity of illness and ICU outcome were also evaluated as well, including; acute kidney injury, respiratory failure, need for vasoactive medication, neutropenia and infection. The NICE definitions were used

to define these parameters (van de Klundert *et al*, 2015); need for renal replacement therapy or a creatinine level over 133 μmol/l in combination with oliguria in the first 24 h of admission was used to define *acute kidney injury*. *Respiratory failure* was defined as the need for mechanical ventilation in the first 24 h of ICU admission. *Neutropenia* was defined as $<0{\cdot}5 \times 10^9$ neutrophils/l and *infection* as a proven infection at admission or within the first 24 h of admission, based on a culture test, positive gram stain, perioperative findings or the physician's judgment.

Statistical analyses

Categorical data were presented as frequencies with corresponding percentages and continuous data as means with standard deviations. The chi-square test was used for categorical variables, the Mann-Whitney U test for non-normally distributed continuous data and the student t-test for normally distributed continuous data. All tests were two-sided and a *P*-value less than 0·05 was considered statistically significant.

To obtain a first impression of a possible trend in time, we compared the prevalence of baseline characteristics between two equal periods of 6 years. The first period comprised the period from 2003 to mid-2009 and the second period from mid-2009 to 2015.

Primary outcome was mortality at one year after ICU admission. Secondary outcome measurements were ICU-, 28 days- and 3 months-mortality. We studied the association between year of admission and one-year mortality with univariate logistic regression yielding crude odds ratios (OR) with corresponding 95% confidence intervals (95% CI) for each category of haematological malignancy. We also performed univariate analyses for all relevant baseline characteristics to clarify a possible trend in time of these variables and the direction of this change. Continuous baseline characteristics were dichotomized, by taking the median (age) or a clinical relevant cut-off point (bilirubin >102 μmol/l and platelet count $< 50 \times 10^9$/l) (van de Klundert *et al*, 2015). Annual ORs were adjusted for the APACHE II score to determine if a possible trend in time was affected by the illness severity of admitted patients. ORs were adjusted, with all variables that had a statistical significant trend in time in the univariate regression model complemented by treating *hospital* in a multivariate analysis. Variables included in the composite APACHE score (age, creatinine level, white blood cell count/neutropenia) were not used again in the multivariate analysis. To give an impression of trends in short term mortality (ICU-, 28 days- and 3 months- mortality), we also created annual ORs and adjusted these for the APACHE II score and hospital in a simple multivariate analysis. Approximated ICU mortality rate (AMR) was calculated with a simplified model based on the APACHE II score without adjustment for admission reason, as haematological malignancy is not a separate admission reason category in APACHE II: APACHE score 0–4 predicts a 4% ICU mortality; 5–9, 8%; 10–14, 15%; 15–19, 25%; 20–24, 40%; 25–29, 55%; 30–34, 75%; and >34, 85%. The expected mortality rates per year were compared with the actual annual ICU mortality rates with use of Wilcoxon signed-rank tests. Missing values were considered as missing in our analyses.

Results

Between 2003 and 2015 a total of 1095 patients were included in our study with a mean age of 53 years in the first time period that increased to 58 years in the second period (Table I). The number of included patients ranged from 20 to 157 per year (Fig. 1). The percentage of females (37%) remained unchanged. The length of stay in the ICU was 8 days and did not change throughout the years. AML was the most frequent haematological malignancy (35%), followed by NHL (30%) and multiple myeloma (13%). The distribution of the type of haematological malignancy remained unchanged throughout the years. Of all patients, 28% received a stem cell transplantation, which was allogeneic in the majority of patients (21% of all patients). The percentage of patients that received an allogeneic stem cell transplantation was lower in the second period of our cohort compared with the first period (16% vs. 24%, respectively). In the first part of our cohort, 32% of the patients were neutropenic, this percentage dropped to 22% in the second period. Thrombocytopenia was less prevalent in the second time period (platelet count have increased) as was a high bilirubin level. No difference in the main admission reason (sepsis) throughout the years was observed. There were fewer patients with anaphylactic shock as admission reason over time, but these numbers are small (12 patients). Almost two-thirds of the patients (64%) received mechanical ventilation within the first 24 h of admission and half the patients needed vasoactive medication. The mean APACHE II score was 22 in the first period and 30 in the second period (overall mean 26).

One-year mortality was 62% during the whole study period. Both short- and long-term mortality were lower throughout the years (Fig. 1, Table II). There was an annual decrease of 4% in one-year mortality (Table III). The annual decrease in one-year mortality was 6% when adjusted for the APACHE II score only and 7% in the multivariate regression analysis. Although there was a trend towards a decreased mortality in all haematological malignancy subtypes, this was only statistically significant in AML patients in which the adjusted annual decrease in mortality was 11%. The effects of the baseline characteristics on the annual change in one-year mortality are also shown in Table III. The one-year mortality decreased in a statistically significant fashion in elderly patients, and patients with a low platelet count ($<50 \times 10^9$/l), bleeding as admission reason, and in those who were mechanical ventilated.

The AMR increased in line with the increase in APACHE II score (Fig. 2). Apart from the years 2004, 2005, 2006 and

Table I. Baseline characteristics with comparison of prevalence between two equal time periods.

		Incidence per period		
Total n = 1095	Incidence N (%) or mean ± SD	2003-mid-2009* (n = 660)	mid-2009–2015 (n = 435)	P-value
Female sex	400 (37%)	37%	35%	0·44
Mean age, years	55 ± 15	53 ± 15	58 ± 14	**<0·01**
Malignancy characteristics				
ALL	76 (7%)	7%	7%	0·96
AML	387 (35%)	36%	34%	0·32
CLL	67 (6%)	5%	7%	0·26
CML	47 (4%)	4%	5%	0·19
HL	44 (4%)	4%	4%	0·63
NHL	329 (30%)	30%	31%	0·76
Multiple myeloma	145 (13%)	14%	12%	0·40
Active disease	692 (63%)	63%	64%	0·98
Stem cell transplantation	307 (28%)	31%	24%	**0·03**
Allogeneic	226 (21%)	24%	16%	**<0·01**
Autologous	81 (7%)	7%	8%	0·52
Admission reason				
Disease-related	198 (18%)	20%	15%	0·06
Sepsis	542 (50%)	50%	48%	0·50
Anaphylactic shock	12 (1%)	2%	1%	**0·03**
Intestinal perforation	34 (3%)	3%	3%	0·60
Pulmonary embolus	15 (1%)	2%	1%	0·30
Neurology	75 (7%)	6%	8%	0·13
Bleeding	71 (7%)	6%	7%	0·85
Toxicity treatment	32 (3%)	4%	2%	0·17
Other	115 (11%)	8%	15%	**<0·01**
Severity of illness				
Mean APACHE II score	26 ± 18	22 ± 10	30 ± 24	**<0·01**
Mean AMR	44 ± 23	41 ± 22	48 ± 25	**<0·01**
Acute kidney injury	167 (15%)	17%	13%	0·11
Vasoactive medication	550 (50%)	51%	50%	0·74
Mechanical ventilation	698 (64%)	62%	66%	0·21
Neutropenia	309 (28%)	32%	22%	**<0·01**
Infection	498 (46%)	48%	42%	0·10
Mean length of ICU stay	8 ± 13	8 ± 13	8 ± 12	0·53
Laboratory variables				
Mean platelet count ($\times 10^9$/l)	90 ± 121	80 ± 98	104 ± 146	**0·04**
Mean bilirubin level (μmol/l)	46 ± 77	51 ± 84	38 ± 66	**<0·01**

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; AMR, approximated mortality rate; APACHE II, Acute Physiology and Chronic Health Evaluation II score; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; ICU, intensive care unit; NHL, non-Hodgkin lymphoma; SD, standard deviation.
*2003-mid-2009 = 2003 to 03-05-2009; mid-2009-2015 = 04-05-2009-2015.
bold, *P-value <0.05 was considered statistically significant*

2008, the AMR was significantly higher than the actual ICU mortality (probability values for the years 2008 until 2015 were <0·01).

Discussion

The main findings of our study are that the mortality of patients with a haematological malignancy admitted to the ICU has decreased over time and that this could not be explained by an admission policy of less critically ill patients. Furthermore, the APACHE II score overestimated ICU mortality in this patient category. This may be due to the absence of haematological malignancy as an admission reason in the APACHE mortality rate calculation (Knaus *et al*, 1985). The AMR and the actual ICU mortality rate differed, especially in the most recent years and particularly in AML patients. This is in line with previous studies, where scoring systems such as the APACHE II were found to have limited value in predicting mortality in haematological patients (Sawicka *et al*, 2014).

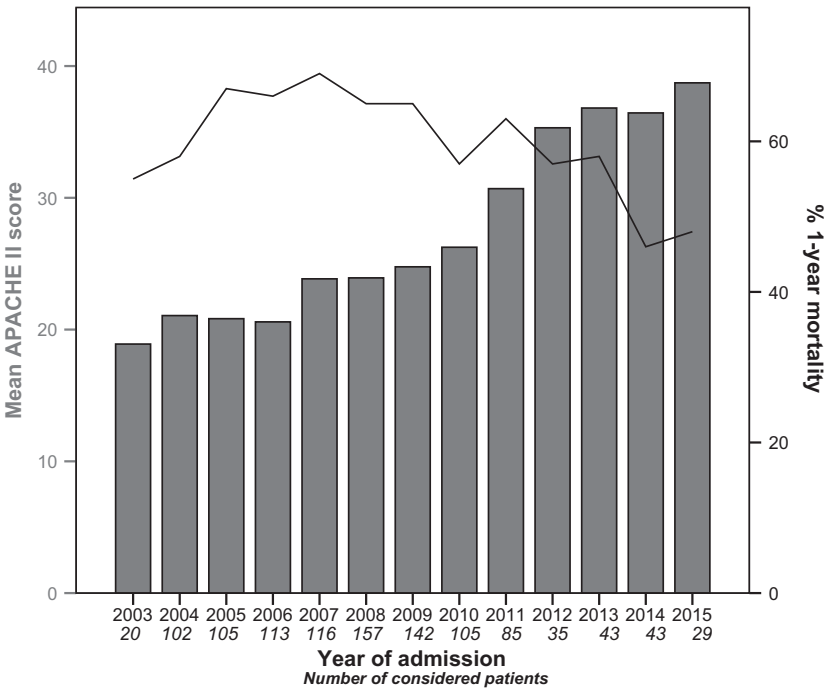

Fig 1. Time trend of 1-year mortality (black line) and the APACHE II score (columns). Considered patients are listed per year. APACHE II, Acute Physiology and Chronic Health Evaluation II score.

Table II. Annual Odds Ratios (ORs) of the secondary outcome variables.

Secondary outcome variables	Adjusted annual OR (95% CI)*
ICU mortality	0·92 (0·88–0·97)
28 days mortality	0·94 (0·90–0·98)
3 months mortality	0·94 (0·90–0·98)

95% CI, 95% confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II score; ICU, intensive care unit; OR, odds ratio.
*Adjusted for hospital and APACHE II score.

Although age is included in the APACHE score, the difference in age in our study population throughout the years hardly influenced for the total score. The less frequent occurrence of neutropenia in recent years may have led to a decrease in APACHE score, as a white blood cell count below three contributes to the APACHE score. The increase in APACHE score is therefore most likely caused by a worsening of physiological parameters, reflecting a more critically ill patient.

There have been developments in both hameatological and critical care support, which makes it difficult to attribute improved morality rates to one of them. The results of our study suggest that mortality rates have decreased in patients with AML, in older patients, in patients with a low platelet count, bleeding as admission reason, and in patients who received mechanical ventilation. Most of these variables, such as AML, age and need for mechanical ventilation, were reported as predictive for mortality in haematological patients admitted at the ICU in previous studies (Bird *et al*, 2012; Namendys-Silva *et al*, 2013; Oeyen *et al*, 2013; Sant *et al*, 2014). This suggests that the chance of survival has increased specifically in 'high risk' patients. The improved survival rates of AML patients may be an indication for better supportive care because the chemotherapeutical treatment of AML has hardly changed in the last decades. Better supportive care may include improvement in critical care, such as lung protective ventilation, the introduction of nationwide implementation of rapid response systems, and restrictive fluid and transfusion policies, which could explain the increased survival chances (Acute Respiratory Distress Syndrome Network, 2000; Ludikhuize *et al*, 2015). The practice of administering prophylactic platelet transfusions using the trigger level of $10x10^9$/l has been shown to be safe and is therefore the standard practice nowadays (Stanworth *et al*, 2013; Estcourt *et al*, 2016). In addition, the prevalence of neutropenia at admission has decreased, as well as the prevalence of thrombocytopenia and high bilirubin levels. These changes may either reflect better haematological care, but more likely reflect a change in the type of patients admitted to the ICU in the different cohorts. Currently, a donor can be found for most adults in need of an allogeneic stem cell transplantation and, more importantly, with introduction of reduced intensity, conditioning (RIC) has meant that older patients can be treated with an allogeneic stem cell transplantation. As a result, the rate of allogeneic stem cell transplantations has increased (Gragert *et al*, 2014). On the other hand, complications related to stem cell transplantations have decreased, such as graft-versus-host-disease, due to better immunosuppression with less toxic effects, e.g., post-transplantation use of high-dose cyclophosphamide or tacrolimus plus methotrexate as graft-versus-host disease prophylaxis (Luznik *et al*, 2010; Bacigalupo *et al*, 2015;

Table III. Annual Odds Ratios (ORs) of one-year mortality.

	Annual OR (95% CI)	Adjusted annual OR (APACHE II)	Adjusted annual OR (multiple regression)*
Haematological malignancy			
All types	**0·96 (0·92–0·99)**	**0·94 (0·90–0·98)**	**0·93 (0·89–0·98)**
ALL	1·00 (0·86–1·19)	1·00 (0·83–1·20)	
AML	**0·92 (0·86–0·99)**	**0·90 (0·83–0·98)**	**0·89 (0·81–0·98)**
CLL	0·95 (0·81–1·12)	0·92 (0·77–1·09)	
CML	0·95 (0·79–1·13)	0·97 (0·81–1·17)	
HL	0·93 (0·77–1·12)	0·95 (0·78–1·16)	
Multiple Myeloma	0·95 (0·85–1·06)	0·95 (0·84–1·07)	
NHL	0·99 (0·92–1·07)	0·96 (0·88–1·04)	
Age (old age >58 years)	**0·94 (0·88–0·99)**	**0·91 (0·86–0·97)**	
Active disease	0·95 (0·90–1·01)	**0·92 (0·87–0·98)**	
Stem cell transplantation	0·99 (0·91–1·07)	0·97 (0·88–1·07)	
Allogeneic	1·01 (0·91–1·13)	1·05 (0·92–1·18)	
Autologous	0·97 (0·85-1·11)	0·86 (0·72–1·02)	
Admission reason			
Disease–related	0·99 (0·96–1·12)	0·98 (0·87–1·10)	
Sepsis	1·01 (0·95–1·07)	0·97 (0·91–1·03)	
Anaphylactic shock	0·69 (0·31–1·55)	0·71 (0·27–1·90)	
Intestinal perforation	0·93 (0·73–1·18)	0·91 (0·71–1·16)	
Pulmonary embolus	1·04 (0·75–1·45)	1·04 (0·75–1·45)	
Neurology	0·87 (0·74–1·03)	0·86 (0·72–1·03)	
Bleeding	**0·75 (0·61–0·92)**	**0·73 (0·59–0·91)**	
Toxicity treatment	0·81 (0·61–1·08)	0·81 (0·61–1·08)	
Other	0·91 (0·81–1·03)	0·89 (0·78–1·01)	
Acute kidney injury	1·04 (0·92–1·18)	0·98 (0·86–1·12)	
Vasoactive medication	0·99 (0·94–1·06)	0·96 (0·90–1·03)	
Mechanical ventilation	**0·93 (0·88–0·98)**	**0·92 (0·87–0·98)**	
Neutropenia	0·99 (0·91–1·08)	0·97 (0·90–1·06)	
Infection	0·99 (0·93–1·07)	0·98 (0·91–1·06)	
Platelet count (<50 x10^9/l)	**0·93 (0·87–0·99)**	**0·89 (0·83–0·96)**	
Bilirubin level (>102 μmol/l)	0·91 (0·79–1·05)	0·93 (0·80–1·08)	

95% CI, 95% confidence interval; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; APACHE II, Acute Physiology and Chronic Health Evaluation II score; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; ICU, intensive care unit; NHL, non-Hodgkin lymphoma; OR, odds ratio.

*Adjusted for APACHE II score, active disease, mechanical ventilation, bleeding as admission reason, platelet count <50 × 10^9/l and hospital.

bold, *significant ORs*

Inamoto *et al*, 2015). This could explain the decreased rate of allogeneic stem cell recipients admitted to the ICU in our cohort.

The strong points of our study are that we only included patients with an acute admission reason and collected a broad range of variables, including haematological characteristics, haematological malignancy type, disease status, neutropenia and laboratory tests. The focus on acute patients only might have negatively influenced survival, but the survival rate was quite comparable with other studies (Benoit *et al*, 2003; Vandijck *et al*, 2008; Azoulay *et al*, 2013; Oeyen *et al*, 2013). Moreover, we focused on long-term outcome instead of short-term outcome and our study covered a long period of time (Thiery *et al*, 2005; Hampshire *et al*, 2009; Taccone *et al*, 2009; van Vliet *et al*, 2014; Grgić Medić *et al*, 2015).

We believe the results of our large heterogeneous study population in a multi-centre design enables our findings to be extrapolated. This is supported by the fact that baseline characteristics, such as APACHE II score, age and rate of stem cell transplantations, were in line with previous European studies (Benoit *et al*, 2003; Vandijck *et al*, 2008; Hampshire *et al*, 2009; Azoulay *et al*, 2013; Oeyen *et al*, 2013; van Vliet *et al*, 2014; Grgić Medić *et al*, 2015; Platon *et al*, 2016).

Our study has also several limitations. The distribution of patients throughout the years is not equal; most of the patients were admitted between 2004 and 2011. This could be explained by the fact that not all centres provided patient information of the first or last couple of years. This could have caused some bias although hospital was not a confounding factor. Another limitation is that we have no detailed information on the patient's hospital course and performance status before ICU admission. More knowledge about treatment failures before or during ICU admission may lead to an adaption of guidelines on the management of critically ill haematological patients and admission policy to ICUs. It is important to identify what criteria are used for ICU

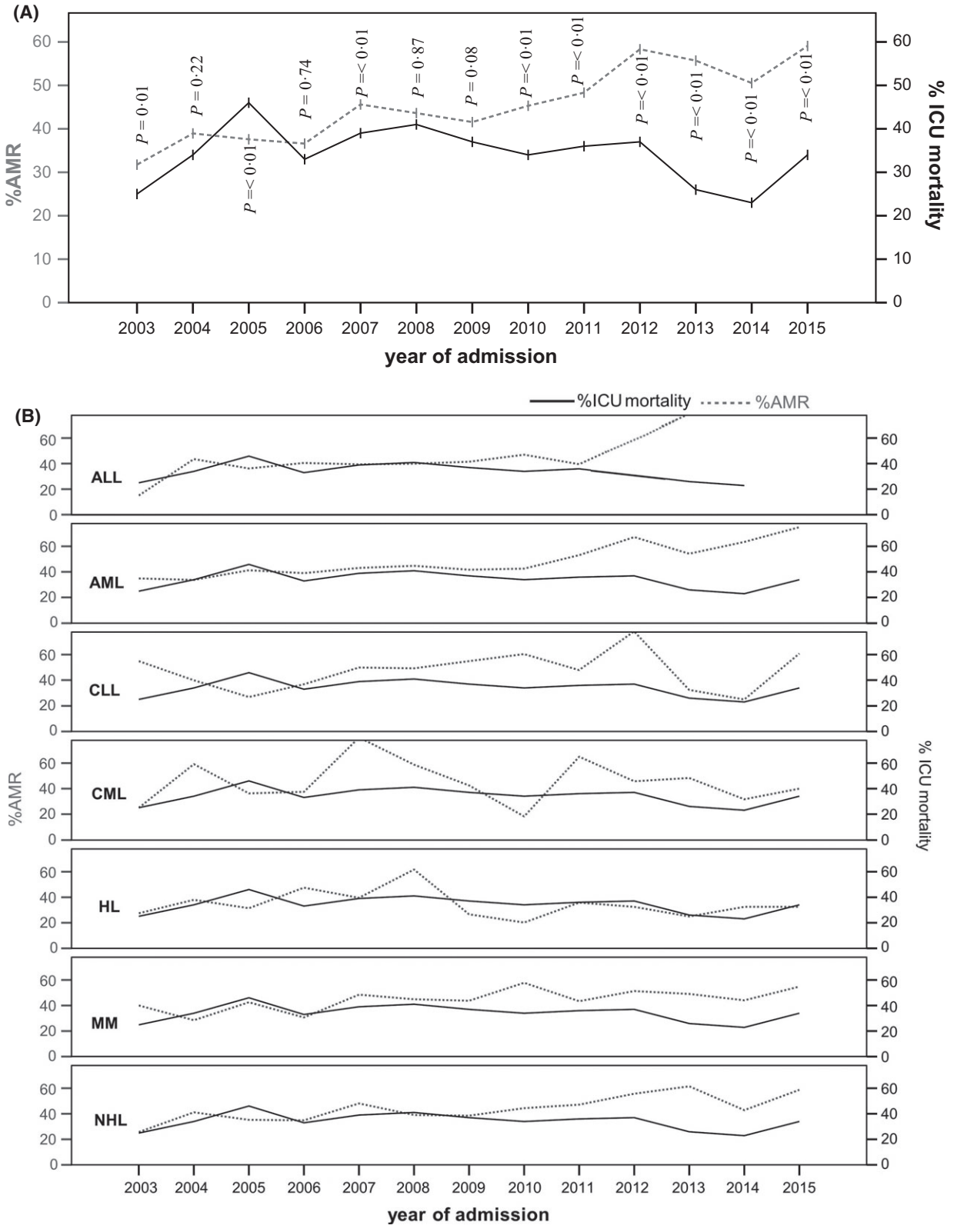

Fig 2. Approximated Mortality Rate compared with the actual ICU mortality rate. A. For all patients (p-values of paired t-tests are displayed in the figure). B. According to haematological malignancy. ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; AMR, approximated mortality rate; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; ICU, intensive care unit; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

admission of patients with a haematological malignancy and to estimate the prognosis of haematological patients at the ICU more accurately. Finally, the definitions we used for organ failure were based on the NICE criteria and could therefore differ slightly from international organ failure definitions, such as the SOFA score (van de Klundert *et al*, 2015).

Conclusion

The outcome of patients with a haematological malignancy admitted at the ICU has improved throughout the years. Although patients had higher APACHE II scores at admission, both long-term and short-term mortality rates have decreased. This is primarily due to a better outcome in AML patients. The decreased mortality rates of high-risk patients suggest improvement in critical care. Furthermore, the APACHE II score overestimates mortality in this patient category.

Authorship contributions

V.A.V: collected, analysed and interpreted data, and wrote manuscript. M.C.A.M, W.M.B.: designed the study, collected, analysed and interpreted data, and manuscript preparation. M.S.A., B.J.B, N.M.A.B, N.K, G.C.W.C, A.P.J.V., D.V.W, H.C.K: collected clinical data, provided important insights and manuscript preparation.

Disclosure of Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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