Outcome Of Hematology Patients In The ICU

A Retrospective Single Center Study

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2017-04-06

Abstract

Objectives: To study the primary outcome of survival of patients with Hematological Malignancies (HM) admitted to the ICU. We identified 86 ICU-admissions and analyzed their patient charts retrospectively.

Design: Retrospective Observational Study

Setting: Intensive Care Unit at a tertiary university hospital

Patients: A total of 76 (86 admissions) consecutive critically ill patients with a hematological malignancy admitted to the ICU between 2011 and 2016.

Measurements: We collected variables from prior to and during admission and identified predictors of in-hospital mortality and long-term outcome with risk ratio analysis and chi-square analysis.

Main Results: SAPSIII for our patient cohort was 72,5 corresponding to an expected in-hospital mortality of 52%. In-hospital mortality in our cohort was lower: 43.5% and correspond to earlier data showing a better outcome for patients with hematological malignancies treated in the Uppsala Akademiska ICU.

Conclusions: The mortality for hematology patients continues to be high. No further factors predicting outcome could be determined from this current study. It continues to be a patient group with a high mortality though knowledge on how to treat these patients is increasing, and their outcomes are improving.

Table of Contents

Populärvetenskaplig sammanfattning

Detta är en studie som tittar på överlevnaden för patienter med blodsjukdomar (hematologiska sjukdomar) som läggs in på intensivvårdsavdelning (IVA). I denna studie var syftet att avgöra hur överlevnaden ser ut för denna patientgrupp och huruvida det finns faktorer som kan hjälpa till att förutsäga hur det går för patienter med blodsjukdomar eller patienter som har stamcellstransplanterats (HSCT) oavsett grundsjukdom.

Skälen till genomförandet av denna studie är flera, primärt är det viktigt att veta att den väldigt intensiva och krävande vård som utförs på patienter som läggs in på IVA är till nytta för patienten. Vi vill även jämföra denna studie med en som utförts 2007 för att jämföra deras resultat och se om en förändring har skett för denna patientgrupp vid just Uppsalas Akademiska Sjukhus.

För att utföra denna studie identifierade vi alla patienter som hade hematologiavdelningen på akademiska som sin hemavdelning, om de lades in på begäran av hematolog eller om de var stamcellstransplanterade, sedan gick vi igenom deras journaler och tittade efter demografiska data som ålder och dödsdatum och kliniska data så som diagnos vid inskrivning och infektionsstatus.

Valet av dessa faktorer baserades på den litteratur som finns på ämnet som var relevant för frågan och skiljer sig lite från de faktorer man tittat på innan då litteraturen visat att vissa faktorer ej varit så relevanta som man trott.

Det vi kommer fram till i denna studie är att överlevnaden för patienter med hematologiska sjukdomar fortsätter att vara sämre än för andra patientkategorier på IVA men att framsteg gjorts. För flertalet faktorer hittade vi inga statistiskt säkerställda samband som kan tyda på att de inte längre påverkar patienters överlevnad då behandlingarna blivit bättre, eller för att patientmaterialet varit för litet för att man ska kunna utröna små skillnader i samband.

Introduction:

Malignant diseases are a leading cause of death in Europe and approximately 20% of these diseases are hematological in origin. Survival for patients with hematological malignancies (HM) have improved (1)(2).

Though many of the advances in treatment of hematological malignancies have a final curative aim they can also have life-threatening complications such as immunosuppression increasing the risk of opportunistic infections, tumor lysis syndrome resulting in acute kidney failure, graft versus host disease (GVHD) and pulmonary dysfunction/infection resulting in acute respiratory distress syndrome (ARDS) (3) (4) (5). All are severe conditions with high mortality rates, and diagnoses that might require admission to the ICU, where their mortality is higher than that of other patient groups (5) (6).

Current problems:

There has been controversy surrounding the admission to the ICU of patients with hematological malignancies as their mortality in the ICU has been higher - and continues to be so - than that of other patient groups even as HM patient outcomes improve (3) (7) (8) (9). This increase presents a challenge in triage. The purpose of this study is to try to determine the different factors that impact patient's outcome in the ICU at Uppsala Akademiska Hospital (UAS) and whether their outcomes have improved compared to a previous study in 2010 (Westberg, Höglund & Kawati 2011).

There are several different factors of studied prognostic value and some of doubtful significance, we will try to study those the literature supports as relevant and try to provide the context in which they are relevant as we look at our patient cohort at UAS.

Recent studies have found that predominantly the need for mechanical ventilation, vasopressor treatment, presence of invasive fungal infection, development of multi-organ failure and high severity of illness scores at admission are additional prognostic factors for mortality among patients with HM (3) (4) (5) (6) (10) (11).

Primary purpose:

The aim of the study was to identify these prognostic factors as studied in the literature and to try to provide the context in which they are relevant to our patient cohort at UAS. At the same time compare the current results with a previous study from (2007-2011) where the same patient group was studied. Our hypothesis was that due to; increase in awareness of the high mortality risk for this patient category, advancement in hematological treatments and early admission to the ICU have improved their outcome.

Method:

No ethical permission was needed to conduct the study since the study falls within the scope of the ICU quality control. On the other hand permission to use patient charts was obtained from the hospital research and development department.

Cohort:

The patient material included all patients treated in the ICU at Uppsala Akademiska Hospital (UAS) between 2011 and 2016 (regardless of age) with a hematological malignancy or HSCT (regardless of the underlying disease for the HSCT). All patients had their referring ward as 50C at UAS, or were requested admission to the ICU by a hematologist. If more than one ICU admission was recorded, we regarded them as one continuous admission if the interval between discharge and readmission was <72h. The data was collected from patient charts.

Question development; which factors prior to admission were relevant and which treatments were required:

The primary outcome analyzed was ICU mortality, the secondary outcomes were in-hospital mortality, 6-month mortality and long-term survival. Other secondary parameters were discerning which factors are significant in assessing patient risk and viability when admitted to the ICU.

Definitions:

Demographic, clinical, and laboratory data from the first day of ICU treatment were used for statistical analysis. Definition of ICU-admission for a patient with more than one admission was an interval of more than 72h after discharge from ICU.

The different parameters we documented were: Hematological Malignancy type, as documented by hematologist in the patient's chart; reasons for admission, as established from the discharge notes from the ICU; whether patients had undergone HSCT and what type of

HCST they received (allogenic or autologous). We also documented time from HSCT to admission to the ICU, and if there was more than one HSCT performed in a patient, we calculated time to ICU from the latest HSCT.

If patients were HSCT we documented whether they had active GVHD as documented in the chart. What their length of stay (LOS) was, both in the ICU and overall hospital LOS.

Further we documented ICU mortality; 30 days post ICU care; within 6 months; > 6 months and current status. The ICU admission date was subsequently used to calculate the survival and outcome of patients.

Simplified Acute Physiology Score (SAPS) III score were calculated during the first 24 hours after admission to the ICU as documented by the admitting intensivist (12).

Neutropenia was defined as absolute leukocyte count <0,5 and thrombocytopenia as <30. In patients with neutropenia we looked at whether the leukocyte count improved (>0,5) upon discharge.

In patients with multiple reasons for admissions (e.g. septic shock and acute respiratory or renal failure), only the most severe condition (e.g. septic shock) was considered as a primary reason for admission. The diagnoses were determined by the admitting intensivist and was documented in the patient's ICU-chart at the time of admission. We documented the primary cause for admission but also secondary causes to determine multiple organ failure. Severe sepsis and septic shock were consolidated in to one category. We also noted whether patients received chemotherapy within 4 weeks of admission to the ICU, whether they were in remission or not as documented by the Hematologist. The documentation of whether the patient was in remission or not as determined by the hematologist was either obtained through the chart or in discussion with a senior hematologist, together with biopsy-answers. As the remission status was not always immediately evident at the time of documentation in the patient's chart. The treatment modalities in the ICU included invasive mechanical ventilation (MV) and non-invasive MV (NIV), successful NIV was defined as NIV not followed by MV at any point during the admission. Renal Replacement Therapy (RRT) as required either in patients with previously documented chronic renal failure or acute onset renal failure at admission. The use of vasopressors (noradrenaline, dopamine, and vasopressin), as determined necessary by admitting intensivist (hypotension not responding to fluid, proven cardiac failure or organic dysfunction). We also looked at whether patients had a positive blood culture up to one week prior to admission and whether they had positive bacterial or fungal cultures in their airways. We considered Staphylococcus Epidermidis-positive cultures as clinically significant if they were treated with Vancomycin or treated as such by the

infectious disease consultants. We also looked at whether patients were CMV positive during admission or not and whether they had any additional positive sterile cultures after the admission to the ICU. Finally, we looked at whether any limits were placed on treatment after admission to the ICU.

Statistical Analysis:
Kaplan-Meier Survival Curves using hazard ratio and SPSS software: IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Values are presented as mean, median and SD. As well as relative risk inference of ICU- and 30-day mortality.

Results:

76 patients were treated between 2011 and 2016 with a total of 86 admissions, 4 admissions were readmissions with less than 72h after discharge from the ICU and were therefore incorporated into one consolidated ICU-admission. Average age was 54,3 years (16-79 years) and the proportion of men to women was 67% vs 33%.

Out of the patients admitted 32 (37,2%) had received HSCT regardless of underlying disease and out of these 26 (81,2%) had received an allogenic transplant. The time the patient received HSCT to ICU admission varied between 0 and 3591 days (median 45 days).

The most common underlying diseases were the acute leukemias (AML, ALL, Burkittleukemia and PML) 36 (41,8%), lymphomas 10 (11,6%) and myelomas/MGUS 10 (11.6%).

57 (66,3%) patients received chemotherapy within 4 weeks prior to admission.

28 patients (32,6%) were neutropenic (defined absolute leukocyte count <0,5) upon admission to the ICU, and 21 out of these (75%) were still neutropenic upon discharge from the ICU. 42 (48,8%) were thrombocytopenic (thrombocyte count <30) upon admission.

15 patients (17%) were deemed to be in complete remission when admitted to the ICU.

Hematological disease n(%)	
AML	22 (25.6%)
ALL	11 (12.8%)
Other acute leukemias (Burkittleukemia, unspec, PML)	6 (6.9%)
Lymphoma	10 (11,6%)
Myeloma	10 (11.6%)
MDS	7 (8.1%)

KLL/KML	9 (10.5%)
Other (autoimmune hemolytic anemia, myelofibrosis, multiple sclerosis, aplastic anemia, thalassemia major, testicular cancer)	11 (12.8%)

Table 1.

Patient Characteristics	
Age	54,3 years (16-79) (median 62)
Age > 65	33 (38,4%)
Women	28 (32,6%)
Men	58 (67,4%)
LOS in ICU	115,85 h (3h-1420h) SD 188,54
LOS in Hospital	41,1 days (median 32,5 days) SD 35,9
HSCT	32 (37,2%)
No HSCT	54 (62,8%)
Allogenic out of pat with HSCT	26 (81,2%), 26 (30,2%)
Autologous =	4 (12,5%), 4 (4,7%)
Complete Remission	15 (17,4%)
Chemotherapy within 4 w	57 (66,3%)
Thrombocytopenia	42 (48,8%)
Thrombocytopenia not analyzed	1 (1,2%)
Leukopenia	28 (32,6%)
Continued leukopenia upon discharge	21 (24,4%)
Positive blood cultures	28 (32,6%)
Septic Shock/Severe Sepsis	33 (38,4%)
SAPS III	72,5 (median 72,0) SD 15,1

Table 2.

Primary diagnosis upon admission to the ICU varied but the predominant diagnoses were septic shock/severe sepsis, respiratory insufficiency and cardiovascular and coagulopathic causes (table 3). Length of stay in the ICU varied between 3 to 1420 hours with a median of

57 hours (SD186 h) and the total number of days hospitalized including the time spent in ICU was 35,9 days (SD 3,9 days).

Main Diagnosis in ICU	Primary
Sever sepsis/septic shock	35 (30.7%)
ARDS	4 (4.7%)
Resp Insuff (incl acute, chronic and resp arrest)	24 (27.9%)
Acute renal failure	2 (2.3%)
Other Infection	2 (2.3%)
cardiac arrest	1 (1.2%)
Cardiovascular/coagulopathic cause – incl GI/intracranial bleed	10 (11.6%)
Neurological event	2 (2.3%)
AKI+sepsis	5 (5.8%)
RI+sepsis	8 (9.3%)
Other*	5 (5.8%)
*hyponatremia, procedure, surgical intervention, intox	

Table 3.

28 (32.6%) patients had positive blood cultures one week prior to their admission to the ICU or during their stay at the ICU. E. Coli and Staphylococcus Epidermidis (KNS, as determined clinically relevant when treated with Vancomycin) were the two most common pathogens. 39 (45.9%) of patients admitted were positive for CMV by PCR analysis.

Positive findings within one week of admission	No.
E. Coli	7
Staphylococcus Epidermidis	4
Klebsiella Pneumoniae	1
Pseudomonas Aeruginosa	1
Propionium Bacterium	1
Saccaromyces Cerviciae	1
Klebsiella Oxytoca	1
Aspergillus-antigen	2
Betaglucan-positivity	1
Alphastreptococcus	1
Rothia Mucilaginosa	1

Positive findings in blood during admission	**No**.
Enterococcus Faecium	2
Staphylococcus Epidermidis	6
E. Coli	1
Pseudomonas Aeruginosa	2
Unspec Gramneg Rod	1
Enterococcus Faecalis	1
Stentophomonas Maltophila	1
Mycobacterium Haemophilum	1
Staphylococcus Aureus	1

Table 4.

Average Simplified Acute Physiology Score III (SAPS III) was 72.5 which corresponds to a predicted in-hospital mortality of 52%. In-hospital mortality in our cohort was 45.3%.

Primary outcome: survival in the ICU

Our primary outcome was ICU-mortality. 24 patients died in the ICU (27.9%), mortality after 30 days was 45.3% or 39 patients. 52 (60.5%) patients had died within six months of their admission to the ICU, and mortality for patients who died after 6 months was 70.9% or 61 patients. 25 (29.1%) went on to survive long term (>6 months).

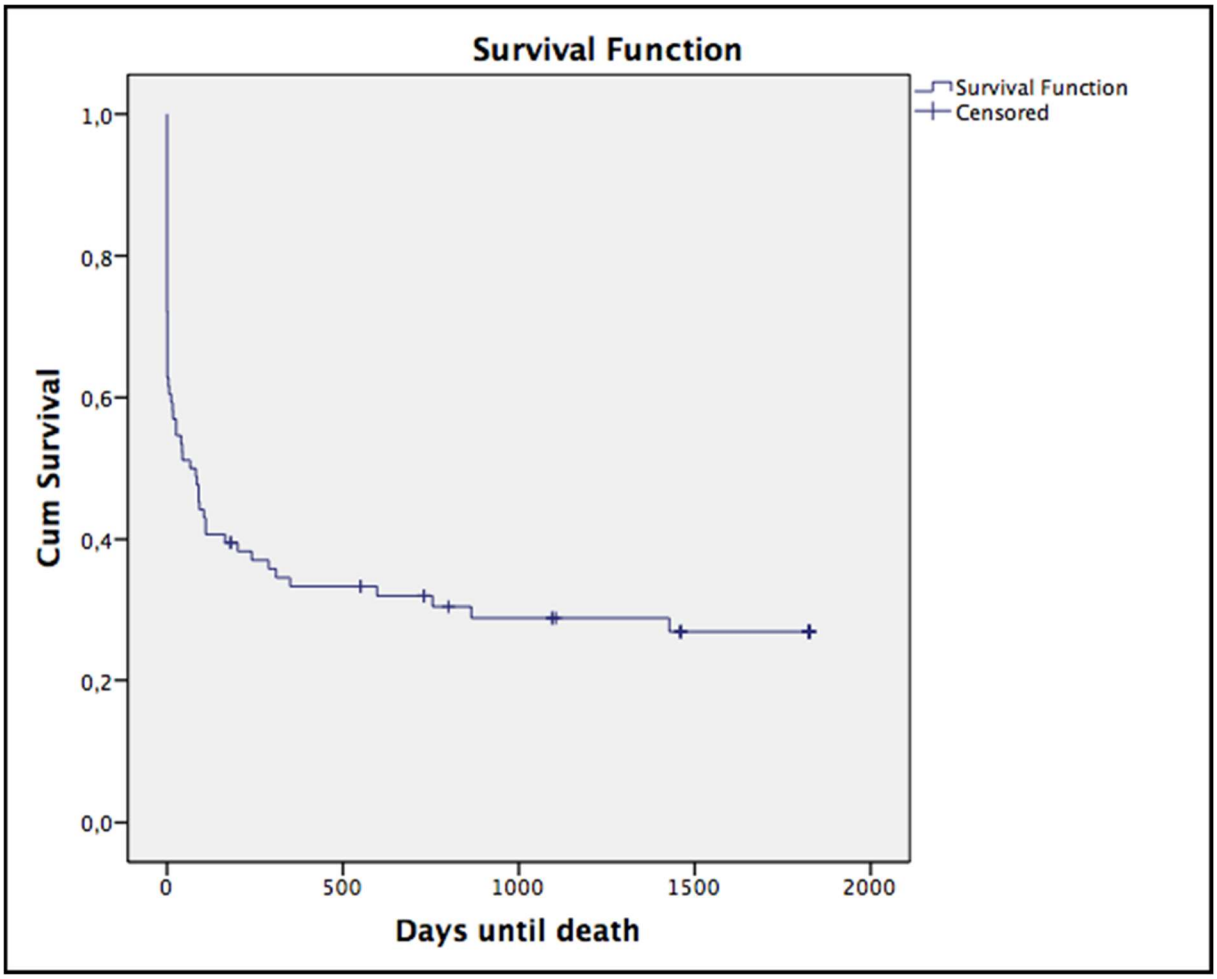

Fig 1. Shows cumulative survival and days until death/end of observation.

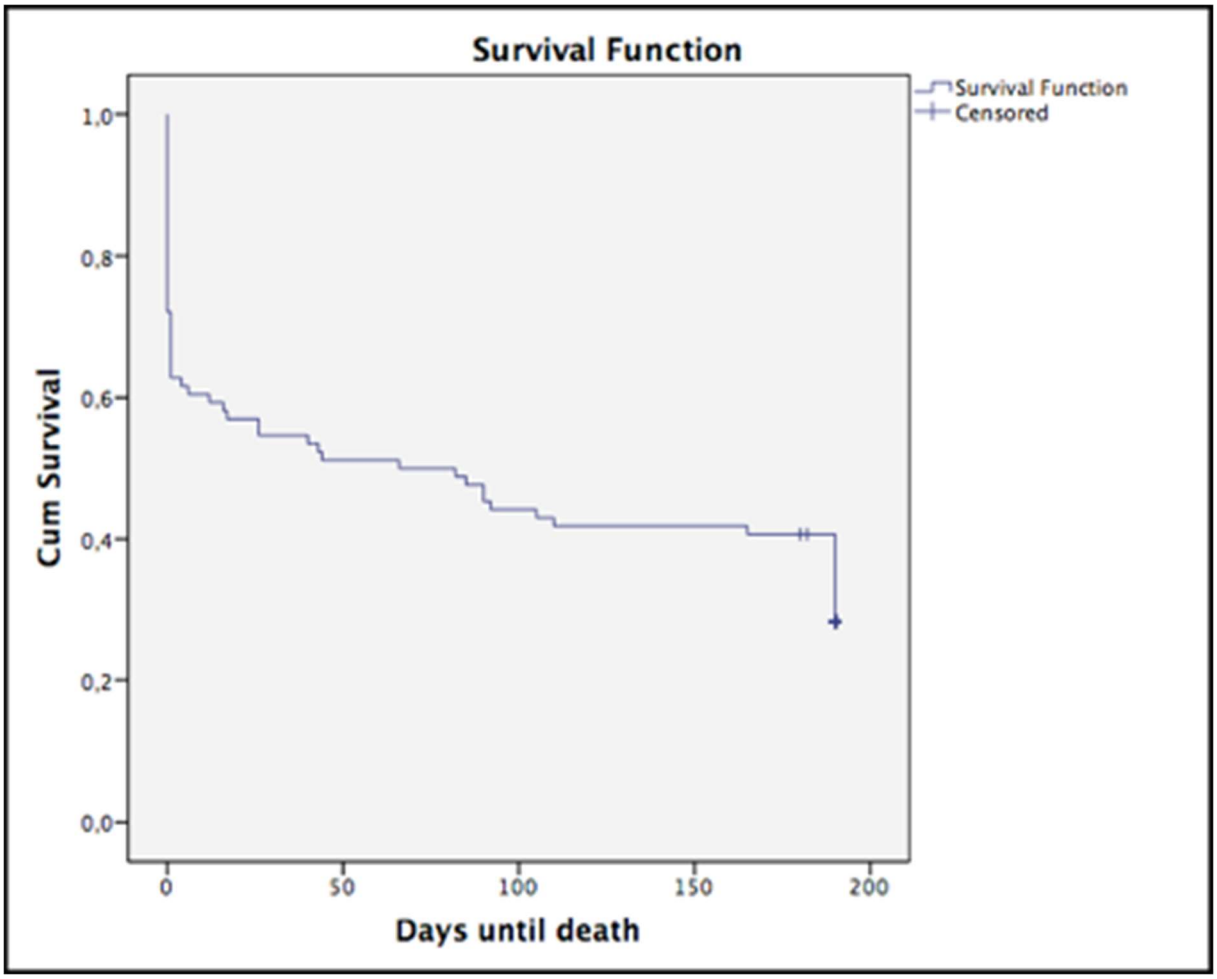

Fig 2. Shows cumulative survival and days until end of observation for long-term mortality > 6 months.

Interventions in the ICU:

40 (46.5%) patients required invasive mechanical ventilation, either upon admission or failure to ventilate adequately with non-invasive mechanical ventilation. 26 (30.2%) patients received renal replacement therapy either as the continuous treatment of their already established chronic kidney failure or as an acute intervention if the patient had developed acute kidney failure. 47 (54,7%) patients received vasopressor treatment. All three factors had a statistically significant increased risk of ICU-mortality and long-term mortality. 19 patients required all three and only one went on to survive for more than 6 months (94.7% mortality). Decisions to limit treatment were made in 32 patients (37,2%) and none of them were alive at the > 6 month follow up.

Whether patients were HSCT or not had no significant impact on mortality, neither had subgroup analyses of whether the HSCT was allogenic or autologous. 15 patients were in

remission and 36 had a prior diagnosis of acute leukemia as determined by hematologist. Neither factor showed statistical significance in outcome. Patients who received chemotherapy within 4 weeks of admission had no statistically significant increase in mortality and the same was true for patients with diagnosed active GVHD. Finally, patients with positive blood cultures either one week prior to the admission or during it had a statistically significant increased risk of poor outcome ($p=0.002$) with a relative risk of 1.46. Overall mortality was at its poorest during the ICU-admission or within 30 days of discharge.

Patients	Mortality in ICU n(%)	Mortality in 30 days n(%)
Total	24 (27.9%)	39 (45.3%)
Age >65	14 (58.3%)	17 (43.6%)
Age <65	10 (16.1%)	21 (33.9%)
Invasive Mechanical Ventilation (IMV)	21 (52.5%)	28 (70.0%)
Non-IMV	3 (6.5%)	11 (23.9%)
Renal Replacement Therapy (RRT) requiring renal failure	12 (46.2%)	17 (65.4%)
No RRT	12 (20.0%)	22 (36.7%)
Inotropes/vasopressors	18 (38.3%)	27 (57.4%)
No Inotropes/vasopressors	6 (15.4%)	12 (30.8%)
IMV+RRT+Vasopressor	10 (52.6%)	15 (78.9%)
HSCT	6 (18.7%)	13 (40.6%)
No HSCT	18 (33.3%)	26 (48.1%)
Allogenic	5 (19.2%)	11 (42.3%)
Non-allogenic	21 (35.0%)	28 (46.6%)
Allogenic	5 (19.2%)	11 (42.3%)
Autologous	1 (14.3%)	2 (28.6%)
Complete Remission	2 (13.3%)	7 (46.7%)
No remission	22 (30.1%)	32 (45.1%)
Chemotherapy within 4 w	19 (33.3%)	27 (47.4%)
No chemo	5 (17.2%)	12 (41.4%)
Acute Leukemia	13 (36.1%)	22 (61.1%)
No acute leukemia	11 (22.0%)	17 (34.0%)
Positive Microbiology	7 (25.0%)	15 (53.4%)
No Positive cultures	17 (29.3%)	24 (41.4%)
Septic Shock	11 (31.4%)	17 (48.6%)
No shock	13 (25.5%)	22 (43.1%)
Active GVHD	2 (18.2%)	5 (45.5%)
No GVHD	22 (29.3%)	34 (45.3%)
Leukopenia	4 (14.3%)	12 (42.9%)
No leukopenia	20 (34.5%)	27 (46.6%)

Table 5.

Mortality post >6 months	No. of Total (%)	>6-month mortality (%)	P-value	Relative Risk (CI)
IMV	40 (46,5%)	32 (80.0%)	0.087*	1.27 (0.9686 to 1.6625)
RRT	25 (29,1%)	23 (92.0%)	0.0008	1.48 (1.1771 to 1.8530)
Inotropes/vasopressors	47 (54,7%)	38 (80.9%)	0.037	1.37 (1.0192 to 1.8440)
IMV+RRT+Vasopressor	19 (22,1%)	18 (94.7%)	0.0002	1.47 (1.1990 to 1.8173)
HSCT	32 (37,2%)	23 (71.9%)	0.88*	1.02 (0.7740 to 1.3479)
Allogenic HSCT	25 (29.1%)	19 (76.0%)	0.48*	1.10 (0.8363 to 1.4569)
Autologous HSCT	7 (8.1%)	4 (57.1%)	0.48*	0.79 (0.4110 to 1.5262)
Not in Remission	71 (82.6%)	49 (69.0%)	0.33*	0.86 (0.6409 to 1.1612)
Acute Leukemia	36 (41,8%)	30 (76.9%)	0.26*	1.17 (0.8922 to 1.5245)
Chemotherapy within 4 w	57 (66,3%)	40 (70.2%)	0.82*	0.96 (0.7315 to 1.2838)
Pos culture	28 (32,6%)	26 (89.7%)	0.002	1.46 (1.1484 to 1.8563)
Active GVHD	11 (12,8%)	9 (81.8%)	0.31*	1.18 (0.8598 to 1.6197)
Leukopenia	28 (32.6%)	19 (22.1%)	0.67*	0.94 (0.6939 to 1.2654)
GVHD	11 (12.8%)	9 (10.5%)	0.30*	1.18 (0.8598 to 1.6197)
Thrombocytopenia	42 (48.8%)	33 (78.6%)	0.13*	1.23 (0.9392 to 1.6232)

***not statistically sign.**

Table 6.

Discussion:

The study showed an increased in long-term (>6 months) mortality compared to patients admitted to the ICU without hematological malignancy as shown in other studies (13) (14). This was particularly pronounced in patients requiring invasive mechanical ventilation (80.0%), renal replacement therapy (92.0%) and vasopressor treatment (80.9%). Comparable figures from the previous study done in the same setting was; IMV (87%), RRT (95%) and vasopressor treatment (85%) (Westberg & Kawati 2010). This correlates to findings in - previous studies evaluating mortality figures for patients with hematological malignancies (3) (10) (15), though the overall figures vary between centers with varied experience with treating

patients with HM (14). In the past few decades the survival of patients diagnosed with hematological malignancies has improved significantly, improving their outcomes (13) (16) (17) (15) (1)(18), possibly leading to a subsequent shift towards increased admissions to the ICU as well (13) (19) (7) (20). Our study had an additional 16 admissions compared to the previous one at the same institution, but we also had a greater time span (5 years compared to 4 years) in which we gathered patient data. Not all studies confirm an increase in admission as a result of improved outcomes (21), and improved triage as a result of better understanding of prognostic factors is a partial explanation (22) (23) (21). It appears to be a difference in outcome depending on the experience of the ICU with treating patients with HM, as a study by Hill et. al showed poor 1-year outcome (79%) for patients treated in the ICU in a study encompassing five institutions (14). They saw no improvement in outcome for patients admitted early on to the ICU. Thus, the improved figures for patients with hematological malignancies admitted to the ICU at Uppsala Akademiska hospital could partially be explained by increased cooperation by intensivists with hematologists and the increased use of mobile intensive groups. Our results show a predicted in-hospital mortality of 52% (with the average SAPS-score of 72.5), yet our observed in-hospital mortality was 43.5% comparing favorably with other centers that have improved their outcomes with the help of better cooperation between specialists and earlier use of mobile intensive groups (3) (13) (15) (24) (10) (11) (25). For ICU admissions the following criteria need to be evaluated: if the condition requiring care in the ICU has the potential of cure/reversal, if the hematological prognosis justifies invasive therapies and, of course, the patient does not decline further treatment. Grounds for admittance need to reflect the known prognostic factors upon admittance.

Neither the previous study done at the same institution (Westberg & Kawati 2011) nor our current study has looked at any form of quality of life data, and therefore wider inferences cannot be made about patient health. A prospective multi-center study from France and Belgium looked at patient outcomes and prognostic factors such as ours, and also at quality of life after 3 months and saw generally good quality of life responses among survivors, another factor to consider in triage (3).

Patients with HM fail to offer the same inflammatory response when treated for severe sepsis compared to patients without HM in the ICU (26) and have benefited from the improved treatment of sepsis to change outcomes (13) (14) (24) (27) (23) (28). In the previous study done at the ICU at the Akademiska Hospital there was no significant result as to whether

positive findings in sterile cultures affected mortality, yet our current data showed a significance in mortality as shown in table 6. Patients with infections who develop sepsis (and they are more likely to develop severe sepsis as a result of their underlying disease (26)) go on to require invasive measures such as vasopressor treatment and dialysis due to hypoperfusion and subsequent multiorgan failure (22) (27) and may therefore still have a greater risk for poorer outcome (6).
In our study we looked at neutropenia and its effects on patient outcomes as neutropenia is both a complication resulting from many of the hematological malignancies studied and the subsequent treatments administered, resulting in patients more susceptible to infection (7). Our data showed no significance (as shown in table 6) in predicting outcome in patients with neutropenia which compares to international data where several studies have shown no significance in outcome in patients with neutropenia (5) (21) (7) (29) (30) (28).

Trying to predict mortality in an individual patient based on subgroup analyses such as the factors we've reviewed above is unrealistic, subgroup analyses as statistical entities where statistical significance can be cautiously inferred leads to the need for conservative conclusions. However, the demands ICU-admissions put on patients and their families also requires careful identification of patients in whom invasive treatments have shown little benefit. Combining the treatment factors IMV, RRT and vasopressor treatment showed a 94.7% mortality risk after > 6 months (a total of 18 patients out of 19 receiving all treatments). The previous study showed a 100% mortality in the same patient group though the patient population is too small to infer statistically significant conclusions on improvements in patient survival.

A factor not evaluated in this study was the time from symptom onset to admission to the ICU, several previous studies have shown an improved outcome in patients with less than 24 h to admission to the ICU or shorter time durations (10) (31). Since the previous study the introduction of mobile intensivist groups has been introduced at Uppsala Akademiska Hospital, these being associated with better triage and earlier admission which could partially explain the improved survival figures. We have gathered no data to be able to infer direct correlation between these units and outcomes, but international studies have shown better outcomes as a result of earlier admissions and introduction of these groups (3) (10).

More aggressive therapeutic advances such as Hematopoietic Stem Cell Transplants (HSCT), targeted therapies such a tyrosine-kinase inhibitors and aggressive chemotherapy regimens has improved survival overall for patients with hematological malignancies (2) (20) (18) (32) (8) (9). With the added challenge of increasingly treating patients aggressively for their primary diagnosis (as patients admitted often receive chemotherapy prior to or during admission (20)) the need for understanding how these treatments can complicate the disease progression as patient prognosis improves increases (33). The previous study and our current follow-up study therefore looked at treatment-related factors such as chemotherapy prior to admission and whether patients developed active GVHD or were in remission. The previous study in 2007 showed a significant risk for patients treated with chemotherapy for up to four weeks prior to admission with an increased long-term mortality (p=0.019), our current study can no longer see a significantly increased risk for our institution and international data is conflicted as to the significance of prior chemotherapy (3) (34). There is a risk for patients with HM who receive chemotherapy to develop tumor lysis syndrome (3) (34), requiring RRT in the ICU a well-documented risk factor (3) (5) (21) (35) (36) (37) (38) and a significant predictor of short and long-term mortality in the study done at our institution in 2007 (relative risk ratio: 1.8, p=0.0003) and again in our current follow-up study (relative risk ratio 1.48, p=0.0008).

The use of Hematopoietic Stem Cell Transplants has steadily increased in industrialized countries (39). Between 13-42% (17) (40) (though figures vary wildly depending on institution) of patients treated with HSCT require admission to the ICU and the primary cause for their admission to the ICU is acute respiratory failure (15) (24) (40) (41) (42).

Mortality increases if patients with hematological malignancy treated with HSCT require Renal Replacement Therapy (RRT) or invasive mechanical ventilation (IMV) (21). If they simultaneously with these two invasive treatments have developed serious Graft Versus Host Disease (GVHD) mortality figures can reach 95% (5) (21) (41). Conversely HSCT is an important part of the treatment and validated improvement have been seen in mortality figures in hematological malignancies (11) (43). In the study from 2007 there was no observed statistically significant risk of poor outcome in patients who received HSCT, yet in sub analysis of patients who received allogenic transplants there was a significance, with a risk ratio of 1.6. We saw no such observed significance in our results in our follow-up study, possibly as conditioning therapies for patients receiving HSCT have improved (42).

Allogenic HSCT as compared to autologous HSCT is associated with higher risk of critical illness, and some studies theorize that increased preconditioning for transplantation in allogenic patients more frequently leads to multiple organ failure (35) (42) (44) as a partial explanation for poorer outcome, as well as allogenic transplants developing GVHD. The previous study from 2007 did not look at active GVHD so no comparable results are available but in our current study 12.8% of patients admitted (table 6) had a documented active GVHD and mortality for them was 81.8% at > 6 months. There was no statistically significant risk associated with active GVHD (p=.30) yet several international studies have shown that active GVDH is associated with multi-organ failure and increased mortality (21) (40) (42). An independent risk factor for patients treated with HSCT to require ICU admission is HLA-mismatch, only seen in allogenic transplants (42). There is increased risk for patients treated with allogenic HSCT to develop GVHD which is an independently poor prognostic factor for these patients and allogenic transplants are a risk factor for HSCT patients to require ICU care (5) (21) (42).

Depending on diagnostic definitions of acute respiratory failure, studies show that patients who are treated with NIMV early on have better outcomes as they do not develop ARDS to the same extent as patients treated with IMV (10) (31), this has however not been confirmed conclusively in subsequent studies (45). In the study from 2007 the correlation between IMV and increased mortality was a significant one (relative risk ratio: 1.7, p=0.0009) and is an independently poor prognostic risk factor in the literature (5) (15) (10) (11) (46) (37) (29). Our data did not show a statistically significant increase in risk for the independent factor of invasive ventilation, but when multifactorial regression analyses were made they showed a markedly significant increase in mortality in patients receiving IMV when analyzed with other covariates such as active GVHD. Patients requiring IMV, RRT and vasopressor treatment continue to have exceedingly poor outcomes (as shown in table 6).

Acute respiratory failure/Acute respiratory distress syndrome is the primary diagnosis for all patients with HM admitted to the ICU (5) (11) (30) with infection being the most common etiology followed by unknown causes (11), in the international literature. Our study found sepsis as defined as severe sepsis or septic shock to be the most common cause for admission followed by respiratory distress, though the two are closely interlinked.

Patients with HM admitted to the ICU are more likely to develop acute renal failure than other patient categories admitted to the ICU (37), and among them patients who receive HSCT treatment are even more likely to develop renal failure and require RRT, especially allogenic

grafts (35) (38). Up until the 2000s treating patients with HM with subsequent acute renal failure with RRT was questioned as mortality figures were so high, since then studies have shown improved outcomes and a study in 2015 with 1011 patients showed a 59.7% mortality rate for those patients requiring RRT (37). This is confirmed in the study from 2007 and subsequently in our follow-up study where patients who require RRT have a relative risk of long-term mortality of 1.48 (p=0.0008), and a significant comorbidity as well. Yet the relative risk has decreased between the two periods of study and in-hospital mortality went down from 77% to 65.4%.

The high association with increased mortality and morbidity in patients with HM treated in the ICU and acute renal failure pinpoints it as an important parameter to consider. The admission to the ICU should be made with regards to the patient's overall prognosis and once they have been admitted, acute renal failure plays a part in determining when further invasive treatment in the ICU is indicated. The different parameters that affect the development of acute renal failure, such as nephrotoxic drugs, HSCT therapy, septic shock, multiple organ failure and tumor lysis syndrome, chronic renal failure prior to admission and other comorbidities such as diabetes and hypertension all play a part in the development of the condition and depending on the underlying cause, outcomes vary. Patients with allogenic HSCT have had stagnant improvements in outcome in the past years and similarly outcomes for patients with septic shock and multi-organ failure who go on to develop acute renal failure and subsequent Renal Replacement Therapy (RRT) remain poor (37). However patients treated with nephrotoxic drugs and those who develop tumor lysis syndrome (even as the risk of tumor lysis syndrome has increased with new and more aggressive therapies) have improved outcomes in recent studies (37) (47). It is therefore an important factor to consider when determining survival in HM patients in the ICU and determining which patients go on to require RRT. Neither the study from 2007 nor our follow up study saw a statistically significant risk in long-term mortality in patients with HSCT, and the patient material has been too small to obtain statistically significant data in multivariate binary regression analyses as to covariates to HSCT in mortality risk analyses.

Vasopressor treatment within the first 24 h of admittance to the ICU was the strongest independent predictor of mortality in a study in 1011 patients in 2015 (11). And continues to be a statistically significant parameter on mortality (15) (6) (41) (48) (25) (26). As the most common reason for patients with HM to require treatment in the ICU in our study was sepsis, an infection with known hemodynamic instability, vasopressors are frequently required (6) in its treatment. The previous relative risk for patients treated with vasopressors was 1.8

(p=0.0009) and continues to a significant factor in our current data with a relative risk of 1.37 a continuously important factor.

Compared to the study from 2007 we used Simplified Acute Physiology Score 3 instead of the previous version 2, there are differences in the two, most notably some recent data that suggests that SAPS 3 overestimates mortality more than its predecessor, though this is not specified for patients with hematological malignancies (49) (50) (12). In the previous study the average SAPS 2 score was 55 which equated to a predicted in-hospital mortality of 58%, observed mortality however was 51%. In our study average SAPS 3 was 72.5 equating to an expected mortality of 52%, our observed in-hospital mortality was however 43.5%, consistent with international data and expected improvements in mortality (12).

The limitations of this study are several, it a retrospective, single-center study which makes its results hard to replicate and apply to other institutions. Only one person did the chart reviews which means that data could be incorrectly interpreted. We also performed multivariate regression analyses, yet our small number of patients gave no significant results as have been shown in other similar multi-center studies (3) (37) (51).The review of literature attempted to use a systematic approach but no explicit plan was written initially, however the factors determining evaluation of the references and literature were the time of publication, to assess the recent advances in the research since the study in 2007. We also looked at the total amount of patients in each study and the applicability of the patients to our own cohort (hematological vs. non-hematological), whether studies were retrospective or prospective and the presented qualities of the different institutions.

Acknowledgments:

I would like to thank my supervisor Dr Rafael Kawati, PhD for his help throughout the writing of this paper.

I would also like to thank Dr Martin Höglund, Professor of Hematology for help with determining remission status in several patients.

Finally thank you statistician Henrik Renlund, UCR for help with the multivariate analyses.

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