

Factors predicting short-term and long-term mortality in ICU patients with a malignancy: the importance of SOFA and ECOG performance status

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Abstract

Background

Intensive Care Unit (ICU) triage decisions in patients with a malignancy can be difficult as clinicians have concerns about potential unfavourable outcomes. Therefore, clinicians may have doubts about the appropriateness of an ICU admission. The aim of this study was to assess the long-term mortality and performance status of critically ill patients with an active malignancy or a malignancy in their prior history admitted unplanned to the ICU. Furthermore, we aimed to compare the long-term mortality of those patients to the mortality of patients without a malignancy.

Methods

We conducted a retrospective cohort study in a large tertiary referral university hospital in the Netherlands. We categorized all adult patients with an unplanned admission to the ICU in 2017 in two groups: 1) the study population consisting of patients with an active malignancy and patients with a malignancy in their medical history (complete remission, CR) and 2) patients without a malignancy. Pearson's Chi-square tests and Independent Samples T-Tests or the Mann-Whitney U tests were used to evaluate the long-term mortality, the primary objective was 2-year mortality.

Results

Of the 1046 unplanned ICU admissions, 125 (12%) patients had an active malignancy, 41 (3.9%) < 5 year CR and 33 (3.2%) \geq 5 year CR. The 2-year mortality in the study population was significantly higher than in the population without a malignancy (67.4% and 40.2%, $P < 0.001$). The median performance status at 2 years after ICU admission in the study population was 1 (IQR 0–2). SOFA score (OR 1.25; 95% CI 1.10–1.42) and ECOG performance status of 2 (OR 11.23; 95% CI 2.66–47.33), 3 (OR 5.91; 95% CI 1.77–19.79) and 4 (OR 13.16; 1.85–93.74) were independently associated with 2-year mortality.

Conclusions

Two thirds of the study population died within 2 years after ICU admission, which is higher than in the population without a malignancy. However, the majority of the study population had a good performance status at 2 years after ICU admission. The severity of the critical illness and the performance status before ICU admission are independently associated with 2-year mortality and should be considered as main factors in ICU triage.

Background

Over the past two decades, the number of patients with a malignancy requiring intensive care treatment has increased (1). Historically, during the 1980's and 1990's, patients with a malignancy were commonly considered ineligible for intensive care treatment due to their presumed unfavourable outcome (2, 3). However, a large European multicentre study shows that nowadays 15% of the patients admitted to the Intensive Care Unit (ICU) are patients with a malignancy (4).

Moreover, the ICU and hospital mortality of patients with an active malignancy has decreased significantly (1, 3, 5). Patients with a solid malignancy show a similar mortality rate compared to critically ill patients admitted to the ICU without a malignancy (6). While literature regarding the mortality of critically ill patients with a hematological malignancy is heterogeneous (7–9), a decrease in mortality over the years has been described (5, 10).

Despite the encouraging trend of survival rates of patients with a malignancy admitted to the ICU, the decision to admit these patients to the ICU remains challenging, especially in the acute setting (11). In an area with rapid evolution of diagnostics and new innovative cancer treatments, reliable literature about short-term and long-term mortality and morbidity of patients with a malignancy admitted unplanned to the ICU is essential, in order to manage outcome expectations of health care providers, patients and families.

Effects of cancer treatment, such as cardiomyopathy or kidney failure, can become clinically evident even decades after completion of therapy (12–16). These effects of cancer treatment could influence the outcome of patients with a malignancy in their medical history admitted to the ICU. However, (long-term) mortality and performance status of patients with complete remission (CR) at the time of an unplanned ICU admission has not been extensively described in literature, except for patients who underwent a stem cell transplantation for a hematological malignancy.

The aim of this study was to assess the long-term mortality and performance status of critically ill patients with an active malignancy or a malignancy in their history admitted unplanned to the ICU. Furthermore, we aimed to compare the mortality in these patients to the mortality of patients admitted unplanned to the ICU without a malignancy. Last, we aimed to identify the factors associated with long-term mortality after ICU admission in patients with an active malignancy or a malignancy in their history.

Methods

We conducted a retrospective cohort study in a large tertiary referral university hospital ICU in the Netherlands. First, we identified all adult patients with an unplanned admission to the ICU in 2017 by using our hospital electronic database. Subsequently, we categorized the patients in two groups: 1) patients with an active malignancy and patients with a malignancy in their medical history (study population) and 2) patients without a malignancy. The study was approved by the ethical committee of our institute (MEC-2018-1172).

We excluded patients with a diagnosis of a non-melanoma skin malignancy (squamous-cell skin cancer or basal-cell carcinoma) because of the relatively favourable prognosis of these tumours, usually without life threatening complications. Similarly, we also excluded patients with a premalignant condition, such as colon polyps.

Patient and ICU characteristics were collected. Patients with a malignancy in their medical history were defined as complete remission (CR), meaning no detectable malignancy based on the information available in the electronic database, medical reports and letters. The 5-year survival rate of patients with a malignancy is commonly used to describe the prognosis of a malignancy (17, 18), we therefore divided patients with CR in CR < 5 year and CR > 5 year. Since late deleterious effects of cancer therapies can occur even decades after completion of the cancer treatment (12–16), we did not exclude patients with a malignancy in their distant past. A metastatic solid malignancy was defined as an solid tumour with the presence of cancer cells present in distant organs or distant lymph nodes, determined by using the medical reports of haematologists and oncologists.

The comorbidity of the patients was measured by using the Charlson Comorbidity Index (CCI) (19). The Eastern Cooperative Oncology Group (ECOG) Performance Status was used to assess performance status in the month to fourteen days before the ICU admission (20). To evaluate the extent of the acute critical illness of the patients at ICU admission, the Sequential Organ Failure Assessment (SOFA) score was used (21, 22). The SOFA score is seen as an useful predictor of outcome (23). Unplanned ICU admissions were defined as medical admissions and postoperative admission after emergency surgery. Readmissions were defined as a new ICU admission within 30 day after discharge from the ICU.

Comfort care was defined as the withdrawal of life-sustaining ICU treatment combined with the initiation of opioids or benzodiazepines when indicated. ICU and hospital mortality were defined as short-term mortality. Long-term mortality was defined as mortality at 6 months, 1 year or 2 years after ICU admission.

The primary objective was to assess 2-year mortality and performance status of critically ill patients with an active malignancy or a malignancy in their history admitted unplanned to the ICU (study population). Furthermore, to compare the mortality of those patients to a patients admitted unplanned to the ICU without a malignancy.

Secondary objectives were ICU and hospital mortality, mortality 6 months and 1 year after ICU admission and to identify factors associated with 2-year mortality after ICU admission in the study population.

Statistical analysis

Descriptive statistics were used to describe patient characteristics, ICU characteristics and mortality in the study population. Categorical variables are reported as numbers with percentage. Continuous variables are reported as mean and standard deviation for normally distributed data or, in case of a skewed distribution, median with 25th–75th interquartile range (IQR).

Primary outcome

Mortality is reported as numbers with percentage. Performance status is reported as mean and standard deviation for normally distributed data or, in case of a skewed distribution, median with 25th–75th interquartile range. To compare the 2-year mortality and relevant patient and ICU characteristics (i.e. age, gender, SOFA score), we used Pearson's Chi-square tests or the Fisher's exact tests for categorical variables and Independent Samples T-Tests (normal distribution) or the Mann-Whitney U tests (skewed distributions) for continuous variables. A statistical test with a two tailed p value ≤ 0.05 was considered as significant.

Secondary outcomes

ICU and hospital mortality, mortality 6 months and 1 year after ICU admission were compared in a similar way as the primary outcome. For an illustrative purpose, a 2- year survival curve was made for the study population and the ICU population without a malignancy. The performance status was reported as median and IQR.

Univariate binary logistic regression was used to assess the association between 2-year mortality and the following variables in the study population: age, gender, ECOG PS before ICU admission, status of the malignancy (i.e. active, CR < 5 year, CR > 5 year), malignancy type (i.e. solid or haematological), admission reason, metastatic solid disease, stem cell transplantation, SOFA score at admission, sepsis and cancer treatment during ICU admission. Subsequently, variables with a p-value < 0.2 in the univariate analysis were evaluated in a multivariate binary logistic regression analysis, except for variables with a small sample size or in case of collinearity.

Missing data were reported as unknown. Data were analysed by using IBM®SPSS® Statistics 24.0 (IBM, Chicago, IL, USA).

Results

In total, 2486 patients were admitted to the ICU, of which 1046 (42%) unplanned admissions. Of these admissions, 221 patients (21.1%) were diagnosed with a malignancy or had a malignancy in their medical history (study population). Patient characteristics are shown in Table 1. – Table 1 is longer than one A4 and is therefore placed at the end of this manuscript. This is the correct place for Table 1 –

Table 1
Patient and ICU characteristics study population

Patient Characteristics	(n = 221)
Age	66 [59–73]
Male	142 (64.3%)
<i>Comorbidity</i>	199 (90%)
No. patients with comorbidity	3 [2–6]
CCI	6 [4–8]
Age-adjusted CCI	2 [1–3]
ECOG performance status	
<i>Type malignancy</i>	172 (77.8%)
Solid malignancy	37 (16.8%)
Hematological malignancy	10 (4.5%)
Both solid and hematological malignancy	2 (0.9%)
Unknown type	
<i>Solid malignancy</i>	101 (45.7%)
Active malignancy	61 (27.6%)
Complete Remission	30 (13.7%)
< 5 year	28 (12.8%)
> 5 year	
<i>Hematological malignancy</i>	21 (9.5%)
Active malignancy	13 (5.9%)
Complete Remission	10 (4.5%)
< 5 year	3 (1.4%)
> 5 year	
Characteristics ICU admission	

Patient Characteristics	(n = 221)
<i>Admission reason</i>	37 (16.7%)
Emergency surgery	180 (81.5)
Medical	4 (1.8%)
Both	56 (25.3%)
<i>Medical admission reasons</i>	35 (15.9%)
Respiratory insufficiency	26 (11.7%)
Postoperative (emergency surgery)	11 (5.0%)
Sepsis	19 (8.6%)
Post cardiopulmonary resuscitation	39 (17.5%)
Neurological (non-traumatic)	35 (16.0%)
Other	
Combination	
Readmissions	58 (26.2%)
SOFA score at admission	7 [5–10]
Mechanically ventilated	140 (63.3%)
Vasopressors	153 (69.2%)
Renal Replacement Therapy	43 (19.5%)
Sepsis during ICU admission	90 (40.7%)
Cancer treatment during ICU admission	10 (4.5%)
Length of ICU stay (days)	3 [1 – 0]

The number of patients with an active malignancy was 125 (56.6%). The majority of the patients were diagnosed with a solid malignancy (172, 77.8%). The different types of the malignancies are shown in supplementary material table 1. The ICU admission reason was mostly medical (81.5%), a quarter of these patients was admitted due to respiratory insufficiency (Table 1).

The 2-year mortality in our study population was 67.4% (Table 2). Two years after ICU admission, the median ECOG performance status in survivors was 1 (IQR 0–2, Table 2), almost 75% of the survivors had an ECOG performance status of 0 or 1.

Table 2
Outcome study population

Mortality	N = 221
ICU	67 (30.3%)
Hospital	97 (43.9%)
6 months	128 (57.9%)
1-year	142 (64.3%)
2-year	149 (67.4%)
ECOG performance status	
Post IC	3 [3–4]
Post hospital	2 [2–3]
6 months post ICU	1 [1–2]
1-year post ICU	1 [1–2]
2-year post ICU	1 [0–2]
ECOG performance status 2-years post ICU	
0	11 (28.2%)
1	18 (46.2%)
2	5 (12.8%)
3	3 (7.7%)
4	2 (5.1%)

The 2-year mortality in our study population was significantly higher than the 2-year mortality in the population without malignancy (40.2%, $p < 0.001$, Table 3). While gender and SOFA score in the study population were comparable to those of the population without a malignancy, the study population was significantly older (Table 3).

Table 3
Characteristics and outcome of study population compared to population without malignancy

	Study population (n = 221)	Without malignancy (n = 825)	P-value
Age	66 [59–73]	56 [44–67]	< 0.001*
Male	142 (64.3%)	519 (62.9%)	0.75
SOFA score at ICU admission	7 [5–10]	8 [6–10]	0.35
SOFA score at ICU death	13 [9–17]	9 [8–13]	0.07
ICU mortality	67 (30.3%)	196 (23.8%)	0.06
Hospital mortality	97 (43.9%)	244 (29.6%)	< 0.001*
6 months mortality	128 (57.9%)	288 (34.9%)	< 0.001*
1-year mortality	142 (64.3%)	305 (37%)	< 0.001*
2-year mortality	149 (67.4%)	332 (40.2%)	< 0.001*
Start comfort care ICU	77 (34.8%)	168 (20.4)	< 0.001*
Start comfort care ward	12 (5.4%)	22 (2.7%)	0.16

The ICU mortality in our study population was 30.3%, which was not statistically significant different from the ICU mortality of the population without a malignancy (23.8%, p 0.06, Table 3). In contrast, the hospital mortality, mortality 6 months and 1 year after ICU admission were significantly higher than in the population without a malignancy. During ICU stay, comfort care was significantly more frequently initiated in the study population than in the population without malignancy (34.8% and 20.4%, p < 0.001). Figure 1 shows a survival curve for illustrative purposes.

The binary univariate logistic regression analysis of the study population yielded a p < 0.2 for the following variables: age, gender, ECOG PS before ICU admission, status of the malignancy (i.e. active, CR < 5 year, CR > 5 year), SOFA score at admission and sepsis during ICU admission (Table 4).

Table 4
Univariate binary logistic regression analysis study population of possible predictors of 2-year mortality

Variable	Patient cases	Mortality	OR	95% CI	P-value
Age	-	-	1.02	0.99–1.04	0.15
Gender (male)	142 (64.3%)	101 (71.1%)	1.59	0.89–2.84	0.12
Comorbidity (CCI)	-	-	1.11	0.98–1.25	0.12
ECOG PS before ICU	46 (20.8%)	22 (47.8%)	-	-	-
0 (ref)	55 (24.9%)	39 (70.9%)	2.66	1.17–6.04	0.02*
1	38 (17.2%)	30 (78.9%)	4.09	1.55–10.80	0.004*
2	51 (23.1%)	37 (72.5%)	2.88	1.24–6.71	0.01*
3	15 (6.8%)	13 (86.7%)	7.09	1.44–35.02	0.02*
4					
Active malignancy (ref)	125 (56.6%)	90 (72%)	0.75	0.35–1.60	0.46
CR < 5 year	41 (18.6%)	27 (65.9%)	0.53	0.24–1.17	0.11
CR > 5 year	33 (14.9%)	19 (57.6%)			
Solid malignancy (ref)	172 (77.8%)	112 (65.1%)	1.45	0.66–3.19	0.36
Hematological malignancy	37 (16.7%)	27 (73%)	2.14	0.44-10.41	0.35
Hematological and Solid	10 (4.5%)	8 (80%)			
Emergency surgery (ref)	37 (16.7%)	25 (67.6%)	0.98	0.46–2.10	0.97
Medical reasons	180 (81.4%)	121 (67.2%)			
Metastatic malignancy	60 (27.1%)	44 (73.3%)	1.38	0.61–3.11	0.45
Stem cell transplantation	12 (5.4%)	10 (83.3%)	2.52	0.54–11.81	0.24
SOFA score	-	-	1.26	1.13–1.40	< 0.001*
Sepsis	90 (40.7%)	68 (75.6%)	1.91	1.06–3.46	0.03*
Cancer treatment during ICU	10 (4.5%)	6 (60%)	0.71	0.20–2.61	0.61

After adjustment for the confounders, an ECOG performance status before ICU admission of 2 (OR 11.23; 95% CI 2.66–47.33), 3 (OR 5.91; 95% CI 1.77–19.79) and 4 (OR 13.16; 1.85–93.74) and SOFA score at admission (OR 1.25; 95% CI 1.10–1.42) were associated with 2-year mortality (Table 5).

Table 5
Multivariate binary logistic regression analysis study
population of possible predictors 2-year mortality

Covariate	OR	95% CI	P-value
Age	1.03	1.00-1.07	0.06
Gender (male)	0.68	0.31–1.49	0.34
CCI	0.91	0.75–1.10	0.32
ECOG PS 0 (ref)	2.27	0.79–6.55	0.13
1	11.23	2.66–47.33	0.001*
2	5.91	1.77–19.79	0.004*
3	13.16	1.85–93.74	0.01*
4			
Active malignancy (ref)	0.93	0.30–2.85	0.90
CR < 5 year	0.42	0.14–1.28	0.13
CR > 5 year	0.50	0.12–2.04	0.33
Active + CR			
SOFA score	1.25	1.10–1.42	0.001*
Sepsis	1.46	0.64–3.35	0.37

Likewise, ECOG performance status before ICU admission of 2 (OR 5.12; 95% CI 1.59–16.49), 3 (OR 5.81; 95% CI 2.36–19.64) and 4 (OR 6.66; 1.59–27.90) and SOFA score at admission (OR 1.19; 1.07–1.31) were independently associated with hospital mortality (supplementary material table 2 and 3).

Factors independently associated with 1-year mortality were age (OR 1.04; 95% CI 1.00-1.07), ECOG performance status before ICU admission of 2 (OR 6.84; 95% CI 1.92–24.42) and 3 (OR 4.16; 95% CI 1.46–11.86) and SOFA score (OR 1.29; 95% CI (1.14–1.45) (supplementary material tables 4 and 5).

No differences in mortality and ECOG performance status after ICU admission between patients with an active malignancy and patients with complete remission were seen (supplementary material table 6). Despite the higher SOFA score in patients with a hematological malignancy, no differences in mortality and ECOG performance status were seen between patients with a solid malignancy and patients with a hematological malignancy, supplementary material table 7.

Both short-term and long-term mortality was significantly higher in patients with an active malignancy than in patients without a malignancy (supplementary material table 8). While long-term mortality was

significantly higher in patients with CR than in patients without a malignancy, no statistical difference in short-term mortality was seen (supplementary material table 9).

Discussion

Clinicians may have doubts about the appropriateness of an ICU admission in patients with a malignancy or a malignancy in their medical history. Reliable literature about long-term mortality and morbidity of patients with a malignancy admitted unplanned to the ICU is essential in order to manage outcome expectations of health care providers, patients and families. We found in our study that a poor functional status as measured by the ECOG performance status, SOFA score at admission and, to a lesser extent, age were independently associated with a poorer short-term and long-term outcome.

Two thirds of the patients with an active malignancy or a malignancy in their medical history die within 2 years after ICU admission. The 2-year mortality of the study population is approximately 1.5 times higher than the 2-year mortality in the population without malignancy. One explanation for this difference could be the weakened condition with a poor ECOG performance status directly after ICU discharge in the study population. The performance status was still reduced at hospital discharge, influencing long-term mortality.

The hospital mortality of our study population was similar to other European literature (44%) (3–5, 24–27). In contrast, the long-term mortality in our study was higher than in other studies (28–34). An explanation may be the difference in case-mix. We included only unplanned ICU admissions, while most other studies included patients with planned ICU admissions as well. Moreover, our study population had a higher SOFA score and received more often organ support.

We found that comfort care was started more often in our study population (35%) than in our population without cancer (20%) and the study population of a specialised Portuguese Cancer institute (13%) (27). Besides differences in case-mix, end-of-life (EoL) decisions could be influenced by many factors, such as religious beliefs, cultural backgrounds, and the ethical climate of the team (35). Consequently, the presence of malignancy or a malignancy in the medical history could influence EoL decisions by clinicians. By starting comfort care, we might spare patients from invasive treatments, such as the insertion of multiple intravenous catheters or prolonged mechanical ventilation, who would have died regardless of ICU treatment. Another explanation exists. Literature shows that prognostication for an individual patient remains difficult (32) and suggests the existence of self-fulfilling prophecy (SFP) in medical decision making, especially in EoL decisions (36). As comfort care inevitable leads to death, we might deprive patients with a malignancy the possibility of prolonged survival if we misjudge the prognosis of an individual patient. To prevent such a misjudgement, EoL decisions should be made in a multidisciplinary meeting.

Within the study population, no statistically significant difference in short-term mortality and long-term mortality was seen between patients with an active malignancy and patients with complete remission. However, a clinically relevant difference in 1-year mortality (67.2% vs 58.2%) and 2-year mortality (72% vs

59.5%) was seen between these groups. This finding suggests that for short-term mortality, other factors such as comorbidity and severity of illness should be considered as important factor for outcome, while the status of the malignancy plays an increasingly important role in long-term mortality. Patients with complete remission showed higher long-term mortality rates when compared to the patients without a malignancy. This finding may suggest an influence of previous cancer treatment (and therefore having a malignancy in CR) on long-term mortality. To our knowledge, the mortality of patients with an active malignancy compared to CR and the general population has not been directly described in the current literature.

Despite the higher mortality, we think it is important to note that the majority of the survivors had a good performance status 2 years after ICU admission, both in patients with an active malignancy as in patients with complete remission. Seventy-five percent of the patients with a known ECOG performance status scored 0 or 1. Our findings are consistent with Zafra and co-workers, in their study 79% of the survivors at 1 year after ICU admission showed an ECOG performance status of 0–2 (37).

The finding that performance status (measured by the ECOG performance status) was independently associated with short-term mortality and long-term mortality (33, 34, 38–40) is in line with other literature. Similar to our study, severity of illness (measured by the SOFA score) has been described in literature as predictor for short-term mortality in patients with a malignancy (30, 31, 41) and long-term mortality (38, 39, 42). Studies which describe SOFA score and performance status as long-term predictor have maximal 1 year of follow up after ICU admission. Our study shows that SOFA score and performance status are independently associated with 2 year mortality as well. To a lesser degree, age was a factor associated with mortality in our study. After an ICU admission, aging is associated with an increased risk of mortality in the 3 years after hospital discharge (43).

As SOFA score and ECOG performance status before ICU admission were independent predictors for short-term mortality and long-term mortality, the decision to deny a patient with a malignancy or a malignancy in their medical history an ICU admission should not solely be based on the presence of a malignancy. Instead, physicians should take the severity of illness and performance status into account before referring or admitting a patient to the ICU. In addition, ICU admission should also depend on the prognostic expectations of the patient. However, prognostication at individual patient level by clinicians remains difficult (1, 32). It is especially difficult in patients with a malignancy, due to the many factors related to the underlying malignancy (e.g. stage, type, hormone receptor status), and the estimation whether the patient will be able to receive future anti-cancer treatment after ICU admission (1, 32). Moreover, poor communication regarding outcome and expectations towards other health care providers or the patient and family has been described, either due to insufficient knowledge concerning prognostication or communication, or due to difficulty with sharing a poor prognosis (32, 44, 45). To improve prognostication and communication, good collaboration with open communication in multidisciplinary meetings and joint education regarding expectations and outcomes is essential (32).

Limitations and strengths

First, the most important limitation is the heterogeneity of the study population. However, by using a binary logistic regression analysis, the heterogeneity of the type of tumour (solid vs hematological) and the status of the malignancy (active vs CR) was minimalized. Literature shows clearly late negative effects of cancer therapies, even decades after completion of the cancer treatment (12–16). We therefore did not exclude patients with a malignancy in their distant past, which caused a wide variation of duration of CR.

Second, selection bias might have influenced our outcome, as our ICU physicians already made an admission decision before ICU admission. Nevertheless, our study population accounted for 20% of the unplanned ICU admissions, which is comparable to other literature. Therefore, the influence of selection bias should be limited.

Third, performance status is not similar to quality of life. However, since literature regarding long-term performance status after ICU admission in patients with a malignancy is very limited, our message of a good long-term performance status is important.

Fourth, data were collected from a single institution, which can restrict generalizability. However our institute is the biggest university clinic in the Netherlands, covering oncologic patient care for a population up to 3 million people.

Last, this was a retrospective study, and all the limitations of a retrospective review could be inherent in our study.

Conclusion

This study shows that two thirds of the patients with an active malignancy or a malignancy in their medical history died within 2 years after ICU admission. Two year mortality in the study population is approximately 1.5 times higher than the 2-year mortality in the population without malignancy. However, the majority of the survivors in the study population had a good performance status 2 years after ICU admission. The severity of the critical illness and the performance status before ICU admission are independently associated with 2-year mortality. Severity of illness, performance status and prognosis should be the main factors in ICU admission decisions.

Abbreviations

Intensive Care Unit (ICU)

Complete remission (CR)

Interquartile range (IQR)

Sequential Organ Failure Assessment Score (SOFA score)

Eastern Cooperative Oncology Group Performance Status (ECOG performance status or ECOG PS)

Charlson Comorbidity Index (CCI)

Odds ratio (OR)

Confidence interval (CI)

End-of-Life (EoL)

Self-fulfilling prophecy (SFP)

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of our institute (Erasmus Medical Center): The Erasmus MC Medical Ethics Review Committee (reference number MEC-2018-1172).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

EZ: conceptualization, design, acquisition, analysis and interpretation of data, writing-original draft and writing- review and editing. LN: data acquisition, analysis and interpretation of data, writing original draft, JE: conceptualization, design, interpretation of data, writing- review and editing, NL: analysis and interpretation of data, writing- review and editing, BW: interpretation of data, writing- review and editing, DB: design, analysis and interpretation of data, writing- review and editing, JB: design, analysis and

interpretation of data, writing- review and editing, EK: conceptualization, design, interpretation of data, writing- review and editing. All authors approved the final manuscript.

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Figures

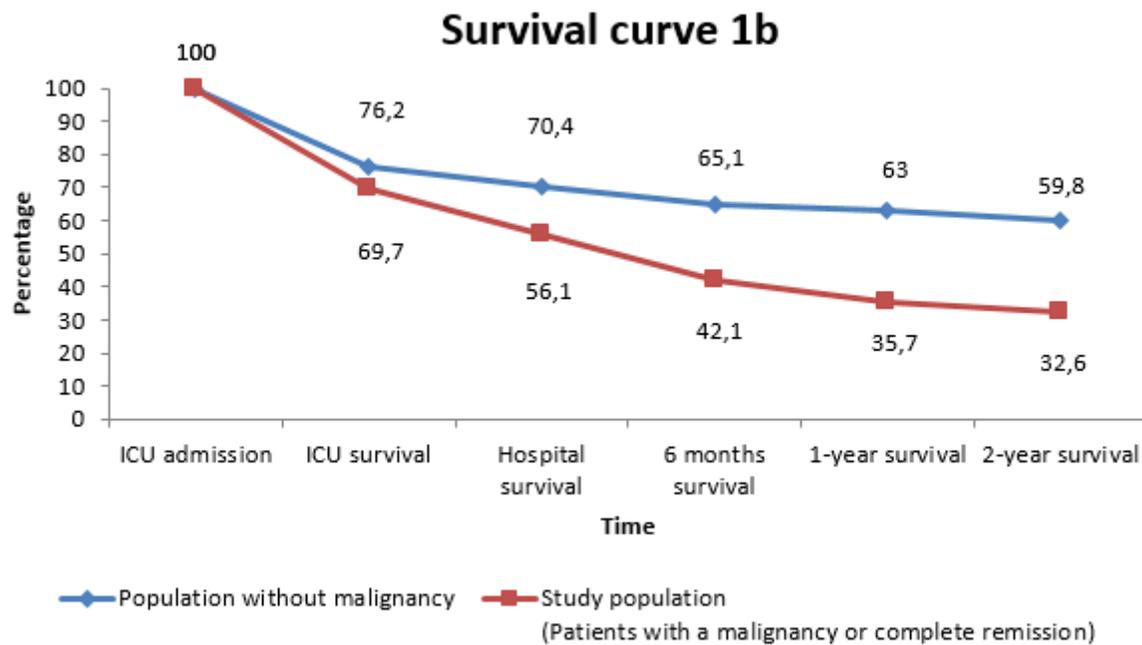
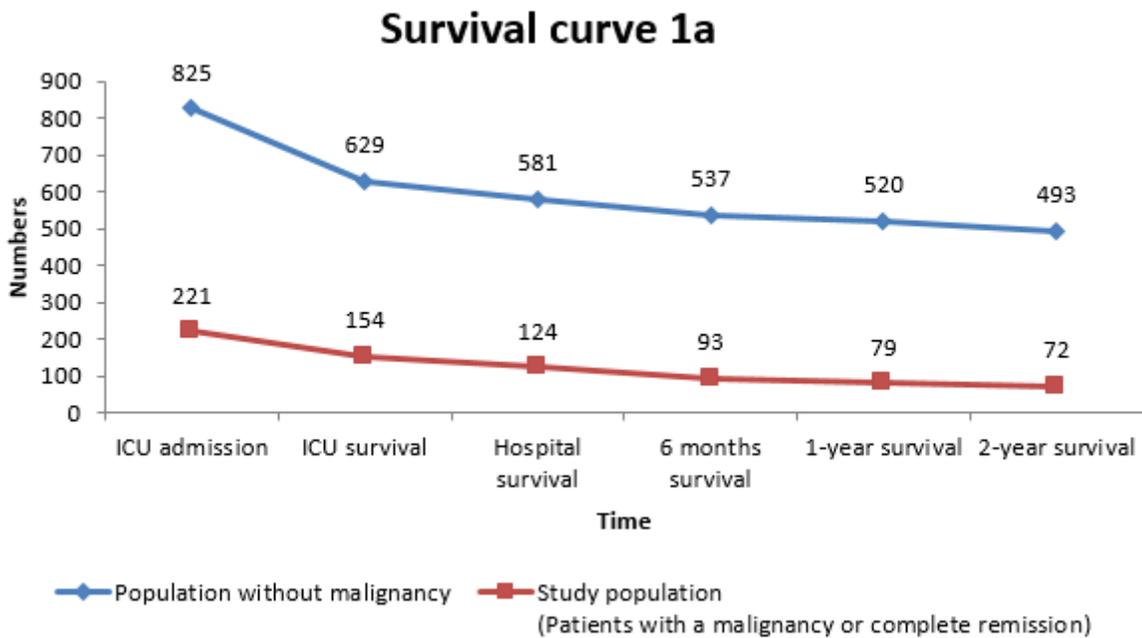


Figure 1

1a: Survival curve 1a. 1b: Survival curve 1b. Survival curve of study population and population without a malignancy in numbers (a) and percentages (b) Legend: Blue line: population without malignancy Red line: study population (patients with a malignancy or complete remission)

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