Trends in Anaesthesia and Critical Care 24 (2019) 13–19

Contents lists available at ScienceDirect

Trends in Anaesthesia and Critical Care

journal homepage: www.elsevier.com/locate/tacc

One-year post-ICU discharge survival among patients receiving long-term intensive care in the University Hospital of Udine, Italy

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ARTICLE INFO

Article history:
Received 19 June 2018
Received in revised form
27 July 2018
Accepted 30 July 2018

Keywords:
Survival analysis
Intensive care
Critical care
Treatment outcome
Italy

ABSTRACT

Our purpose was to assess one-year survival of adult patients discharged from the general Intensive Care Units (ICU) of the University Hospital of Udine, Italy, after a long-term ICU treatment.

For this population-based retrospective cohort study, we used the administrative databases of the Hospital of Udine as the source of information. The cohort included all patients discharged alive from the ICU from 2006 to 2015 after an ICU stay >72 h. Subjects included in the cohort underwent a 365 days follow-up after ICU discharge. One-year survival was analyzed through Kaplan-Meier curves, stratified by hospital discharge main diagnosis. Multivariate Cox regression was used to assess the likelihood of death associated with characteristics of patient and hospitalization, adjusting for the potentially confounding effect of each factor on the others.

Of 2712 ICU patients, 22.9% died in ICU. Among the 2090 survivors, 9.3% died in the hospital and 17.5% died after discharge home. One-year post-ICU discharge survival in the cohort was 70.3% and the steepest decrease was observed in the first weeks. Great variability was observed for different hospital discharge diagnoses. After adjusting for confounders, the Hazard Ratio was significantly associated with age, comorbidity, length of stay, year of hospital admission.

In our study, one-year post-ICU survival was affected by type and severity of illness, patient's age and comorbidities. This study assessed survival and prognostic factors for ICU patients in an Italian Hospital. Quality of life of ICU survivors should also be investigated.

1. Introduction

Intensive Care Unit (ICU) patients have high in-hospital mortality, both in the ICU and after ICU discharge. In USA, Zimmerman et al. reported an 11% in-hospital mortality for ICU patients in 2010–2012, with great variability depending on the underlying clinical condition [1]. Mortality is even worse in lower income countries [2] and prevention of short-term mortality has been one of the main purposes of ICU treatment of these patients. Nevertheless, the 2002 Brussels Roundtable, "Surviving Intensive Care", highlighted also the importance of long-term outcomes evaluation, whose knowledge could orient and influence ICU care decisions [3]. Accordingly, an increasing number of studies concerning long-term survival in ICU patients is appearing in the international literature [2,4–8].

To our knowledge, Italian ICUs were included in a recent European multicenter study of in-hospital mortality [9], but no research has been conducted in this country concerning long-term survival after ICU discharge. Thus, we conducted a study investigating long-term survival in addition to in-hospital mortality for patients treated for more than 72 h in our ICUs, as done by Steenbergen et al. in the Netherlands [7]. In addition, we studied factors associated with mortality.

2. Materials and methods

This population-based retrospective cohort study used as a source of information the Health Information System of the Health District named "Azienda Sanitaria Universitaria Integrata di Udine" (ASUIUD). The Health Information System includes several health-related administrative databases which can be linked with one another at the individual patient level through an anonymous univocal stochastic key. For this study, we used the residence

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https://doi.org/10.1016/j.tacc.2018.07.011
2210-8440/

address database, the hospital discharge database and the mortality database retrieving information on residents in the area of the ASUIUD (37 municipalities with approximately 250,000 inhabitants). The population of this area refers to the University Hospital of Udine for health assistance. Udine Hospital is an Institution with 1000 beds. All medical and surgical specialties are represented, including heart, liver and kidney transplant activity. Udine Hospital also serves as a regional trauma center. There are three general ICUs, with a total of 28 general ICU beds with a nurse-to-patient ratio of 1:2 during day activity and 1:3 during the night.

We built a cohort including all subjects ≥18 years of age, living in the area referring to Udine Hospital, who were discharged alive (either transferred to other Units or discharged at home) from ICUs between January 1st, 2006 and December 31st, 2015, and spending more than 72 h in the ICU.

For each subject, we collected information regarding sex, age at hospital admission, any hospitalizations in the 365 days before the index hospitalization (i.e., the one including the ICU stay), ICD-9-CM codes for discharge diagnoses and procedures, overall length of stay, and ICU length of stay for the index hospitalization.

From the discharge diagnoses recorded in the 365 days prior to the index hospitalization, we calculated Charlson comorbidity score [10], which predicts the risk of death from comorbid disease and is useful in longitudinal studies.

We grouped patients into clinically coherent discharge condition categories by using AHRQ Clinical Classification System (AHRQ-CCS) [11], referring to the principal discharge diagnoses. Procedures recorded with ICD-9-CM codes 96.70, 96.71, 96.72 (corresponding to mechanical ventilation) were abstracted to assess whether mechanical ventilation was provided during the hospitalization.

Subjects included in the cohort were followed for 365 days after ICU discharge, or until change of residence outside the area of interest, or death, identifying relevant events from the administrative databases. Differences in the proportion of one-year deaths between groups of patients were tested through the chi-squared test. Differences in continuous variables between subjects with different vital status at one year were tested though the Wilcoxon's rank Sums tests. One-year survival was analyzed through Kaplan-Meier curves, stratified by AHRQ-CCS diagnosis, and, within each diagnosis, age differences were tested through the log-rank and Wilcoxon's tests. For these analyses, age was categorized into the following 4 groups: 18–44, 45–64, 65–79, ≥80 years. Length of stay was classified into 4–28 days vs > 28 days; ICU stay into 4–7, 8–14, and >14 days. Two-sided p-values <0.05 were considered statistically significant.

Multivariate Cox regression was used to assess the risk of death associated with various characteristics of the patient and of the hospitalization. Covariates included in the model were sex, age, Charlson comorbidity score, AHRQ-CCS diagnosis, overall length of stay, ICU length of stay, mechanical ventilation as indicated by the corresponding ICD-9-CM codes, and year of discharge. To account for the possible intraclass correlation within diagnosis groups, we repeated the analysis using AHRQ-CCS diagnosis as a clustering variable. Hazard ratios (HR) were calculated as the measures of association, and precision of the estimates was expressed through 95% confidence intervals (95%CI).

All the analyses were conducted with SAS v9.4 (SAS Institute Inc, Cary, NC, USA).

2.1. Ethical statement

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Since all the analyses were based on completely anonymous administrative data, Ethics Committee approval was not required in Italy and collection of informed consents from patients was not needed.

3. Results

In the 10-year period of interest, 2712 residents in the 37 municipalities of the ASUIUD area were admitted to the Hospital of Udine and spent more than 72 h in the ICU. They represented 46% of all patients with an ICU stay during the study period. Overall, the median ICU stay in the Hospital of Udine was 62 h (25th percentile: 22, 75th percentile: 185 h). Out of patients with ICU stay >72 h, 622 died during the ICU stay (22.9%). The remaining 2090 were considered as *ICU survivors* and 252 of them (12.0% of ICU survivors, or 9.3% of the whole group population) died in the hospital after ICU discharge, resulting in 874 in-hospital deaths (32.2% of all 2712 patients). Additionally, 366 subjects died after being discharged home.

Among the 2090 *ICU survivors*, fourteen (0.7%) moved outside the study area and 618 died in the first year after ICU discharge (29.6%). In Table 1 we described the characteristics of our cohort.

The proportion of subjects who died in the first year after ICU discharge was similar between females (29.2%) and males (29.8%, $p = 0.80$). Among patients who had mechanical ventilation, one-year mortality (32.3%) was much higher than among the others (25.9%, $p = 0.0017$). On average, age was significantly higher among those who died within 365 days than among one-year survivors (median 75 vs 65 years, $p < 0.0001$), as well as Charlson comorbidity score (median 2 vs 1, $p < 0.0001$). Overall in-hospital and ICU length of stay were slightly higher for patients who died (median 31 and 9.8 days, respectively) than among the others (28 and 7.9 days, respectively; $p = 0.0014$ and 0.0183). The number of in-hospital deaths and after discharge deaths by AHRQ-CCS diagnosis category is displayed in Fig. 1 for categories with at least 5 deaths.

One-year global survival in the cohort was 70.3%. Survival by AHRQ-CCS diagnosis group for conditions with at least 5 cases each is shown in Table 2.

Overall, one-year survival inversely related with age (Fig. 2): 96.3% for 220 patients 18–44 years, 81.7% for 598 patients 45–64 years, 64.4% for 901 subjects 65–79 years, and 51.1% for 371 subjects ≥80 years of age (p-value of both log-rank and Wilcoxon's test <0.0001). In all age groups, high mortality was observed in the first 30 days after ICU discharge, accounting for 37% of mortality in the age groups 18–44 and 45–64, for 40% in the age group 65–79, and for 51% in the elderly group ≥80 years.

The HRs for death in the 365 days after ICU discharge estimated through multivariate Cox regression are shown in Table 3. The analysis using age, overall in-hospital and ICU length of stay as continuous variables yielded very similar results (not shown). In the model taking into account the possible cluster effect of diagnosis, the fixed effects were also very similar (not shown). In that model, the random effects were statistically significant ($p = 0.0054$).

Of all ICU survivors who died within 365 days after ICU discharge, only 54 died at home (8.7%). The others died either in hospital (83.4%), in nursing homes (5.9%), or in hospice (1.8%). 573 subjects died from non-violent causes; groups of causes of deaths are shown in Fig. 3.

4. Discussion

To our knowledge, this is the first Italian study that investigated one-year post-ICU discharge mortality among patients who spent more than 72 h in a general ICU. This particular group of patients

Table 1
Characteristics of the cohort of patients hospitalized from 2006 to 2015 at the University Hospital of Udine, Italy, who spent more than72 h in Intensive Care Unit and were discharged alive from Intensive Care Unit.

Characteristic	Total N = 2090
Female sex – N (%)	739 (35.4)
Age - mean ± std, median (IQR)	65.7 ± 15.3, 69 (58–77)
Charlson comorbidity score - mean ± std, median (IQR)	1.6 ± 2.0, 1 (0–2)
Overall length of stay - mean ± std, median (IQR)	36.8 ± 28.8, 29 (18–46)
Hours in ICU - mean ± std, median (IQR)	312 ± 307, 206 (119–388)
Mechanical ventilation – N (%)	1196 (57.2)
AHRQ CCS diagnosis	
Adult respiratory failure – N (%)	214 (10.2)
Acute cardiovascular disease – N (%)	177 (8.5)
Intracranial injury – N (%)	134 (6.4)
Pneumonia – N (%)	110 (5.3)
COPD – N (%)	72 (3.4)
Crush injury – N (%)	68 (3.2)
Other fracture – N (%)	58 (2.8)
Aneurysm (aortic, abdominal, thoracic) – N (%)	53 (2.5)
Acute myocardial infarction – N (%)	53 (2.5)
Other gastrointestinal disorders – N (%)	44 (2.1)
Shock – N (%)	40 (1.9)
Intestinal obstruction – N (%)	39 (1.9)
Fracture of leg – N (%)	38 (1.8)
Septicemia – N (%)	37 (1.8)
Congestive heart failure non-hypertensive – N (%)	34 (1.6)
Cardiac arrest – N (%)	31 (1.5)
Colon cancer – N (%)	30 (1.4)
Epilepsy – N (%)	28 (1.3)
Coma/brain damage – N (%)	26 (1.2)
Other liver disorders – N (%)	26 (1.2)
Peritonitis – N (%)	26 (1.2)
Biliary diagnosis – N (%)	24 (1.1)
Other lower respiratory disease	22 (1.0)
Esophageal cancer – N (%)	21 (1.0)
Hip fracture	21 (.0)
Others involving <1% of cohort each – N (%)	664 (31.9)

Abbreviation: sstd = standard deviation; IQR = interquartile range (25th percentile – 75th percentile of the distribution); AHRQ-CCS=Agency for Healthcare Research and Quality - Clinical Classifications Software; COPD = chronic obstructive pulmonary disease.

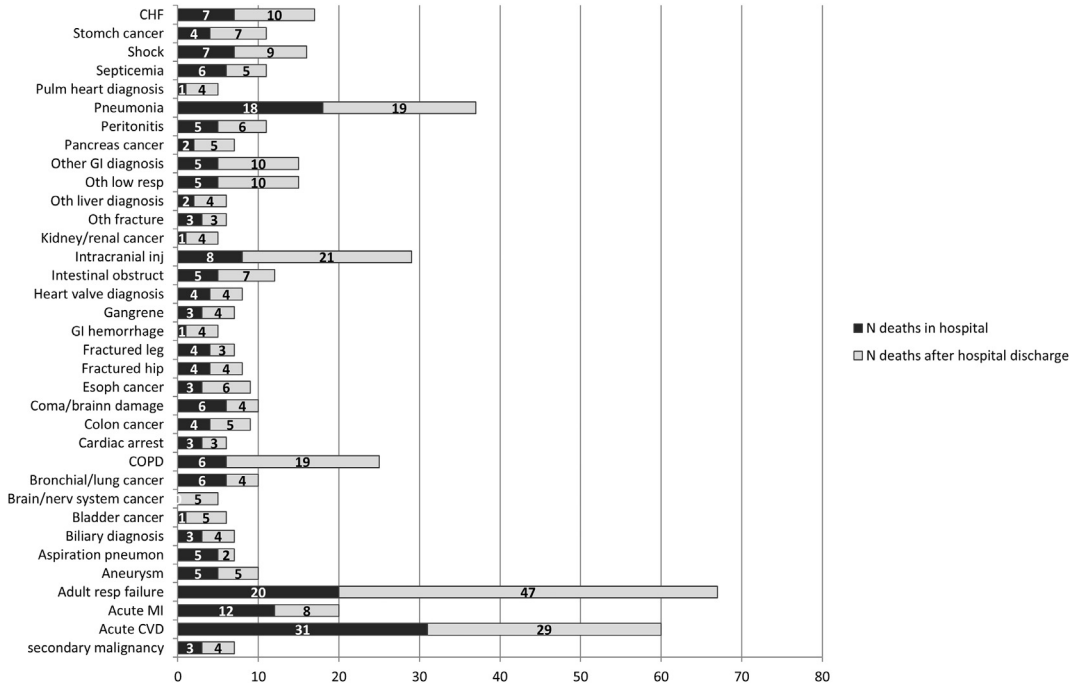

Fig. 1. Distribution of in-hospital and after hospital discharge deaths by AHRQ-CCS diagnosis for diagnoses with more than 5 deaths each.
Abbreviations: AHRQ-CCS=Agency for Healthcare Research and Quality - Clinical Classifications Software; COPD = chronic obstructive pulmonary disease.

Table 2
One-year survival and confidence limits for groups of diagnoses of patients admitted to the University Hospital of Udine, Italy, from 2006 to 2015, who spent more than72 h in Intensive Care Unit and were discharged alive from Intensive Care Unit (only diagnosis groups with at least 5 cases).

AHRQ-CCS discharge diagnosis group	N	1-year survival (%)	95%CI
Aspiration pneumonitis	9	12.5	0.6–42.3
Cancer of brunchus or lung	14	28.6	8.8–52.4
Secondary malignancy	10	30.0	0.7–57.8
Gangrene	10	30.0	0.7–57.8
Other lower respiratory disease	22	30.7	13.1–60.3
Stomach cancer	18	38.9	17.5–59.9
Kidney cancer	9	44.4	13.6–71.9
Bladder cancer	11	45.4	16.7–70.7
Pancreas cancer	13	46.1	19.2–69.6
Heart valve disorder	15	4.67	21.2–68.7
Gastrointestinal and peritoneal cancer	6	50.0	11.1–80.4
Other infections of central nervous system	8	50.0	15.2–77.5
Congestive heart failure, non-hypertensive	34	50.0	32.4–65.2
Brain/nervous system cancer	11	54.5	22.9–78.0
Gastrointestinal hemorrhage	11	54.5	22.9–78.0
Pulmonary heart disease	11	54.5	22.9–78.0
Esophageal cancer	21	57.1	33.8–74.9
Peritonitis	26	57.6	36.8–73.9
Encephalitis	5	60.0	12.6–88.2
Hip fracture	21	60.0	35.7–77.6
Head/neck cancer	10	60.0	25.3–82.7
Shock	40	60.0	43.2–73.2
Tuberculosis	5	60.0	12.6–88.2
Coma/brain damage	26	61.5	40.3–77.1
Acute myocardial infarction	53	62.3	47.8–73.7
Cancer of rectum/anus	8	62.5	22.9–86.1
COPD	72	65.3	53.1–75.0
Acute cardiovascular disease	177	65.9	58.4–72.4
Other gastrointestinal disorder	44	65.9	49.9–77.8
Pneumonia	110	66.4	56.7–74.3
Carditis	9	66.7	27.2–87.8
Neoplasm unspcified	6	66.7	19.5–90.4
Other bacterial infections	6	66.7	19.5–90.4
Esophageal disorders	7	68.6	21.3–91.2
Adult respiratory failure	214	68.6	61.9–74.4
Intestinal obstruction	39	69.2	52.2–81.2
Colon cancer	30	70.0	50.3–83.1
Septicemia	37	70.3	52.8–82.3
Biliary disorder	24	70.8	52.8–82.3
Dysrhythmia	7	71.4	25.8–92.0
Acute renal failure	11	72.7	37.1–90.3
Pancreas disorder	15	73.3	43.6–89.0
Gastroduodenal ulcer	8	75.0	12.8–96.0
Other liver disorder	26	76.9	55.7–88.9
Peripheral atheropathy	13	76.9	44.2–91.9
Intracranial injury	134	78.3	70.3–84.3
Alcohol-related disorders	14	78.6	47.2–92.5
Hypertension complications	5	80.0	20.4–96.9
Other circulatory disorder	5	80.0	20.4–96.9
Cardiac arrest	31	80.6	61.9–90.8
Aneurysm (aortic, abdominal, thoracic)	53	81.1	67.8–89.4
Fracture of leg	38	81.6	65.2–90.8
Chronic kidney disease	17	82.3	54.7–93.9
Other benign neoplasm	17	82.3	54.7–93.9
Cancer of liver and intrahepatic bile duct	12	83.3	48.2–95.5
Coronary atheropaty	20	83.3	56.8–94.3
Other nutritional disorder	12	83.3	48.2–95.6
Coronary atheropathy	20	84.2	58.6–94.6
Abdominal hernia	13	84.6	51.2–95.9
Complication of device	13	84.6	51.2–95.9
Other nervous disorder	13	84.6	51.2–95.9
Skin infection	7	85.7	33.4–97.8
Pleurisy	15	86.7	56.4–96.5
Epilepsy	28	89.1	70.0–96.4
Other fracture (no skull, leg, arm, joint, hip)	58	90.0	78.4–95.2
Meningitis	11	90.9	50.8–98.7
Fracture of skull	12	91.7	53.9–98.8
Spinal cord injury	16	93.7	63.2–99.1
Crush injury	68	94.1	85.1–97.7
Abdominal pain	13	100.0	100.0–100.0
Fracture of arm	12	100.0	100.0–100.0
Joint injury	10	100.0	100.0–100.0
Other injury	10	100.0	1.000–1.000

Abbreviations: AHRQ-CCS=Agency for Healthcare Research and Quality - Clinical Classifications Software; 95%CI = 95% confidence interval; COPD = chronic obstructive pulmonary disease.

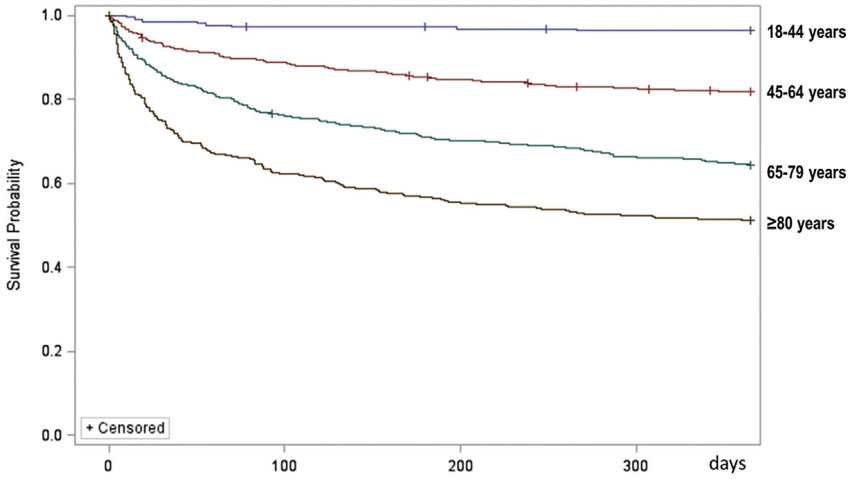

Fig. 2. Kaplan-Meier curves for survival in the 365 days after discharge in a cohort of patients admitted to the University Hospital of Udine, Italy, from 2006 to 2015, who spent more than 72 h in Intensive Care Unit and were discharged alive from Intensive Care Unit.

Table 3
Multivariate Cox regression for one-year mortality among patients admitted to the University Hospital of Udine, Italy, from 2006 to 2015, who spent >72 h in Intensive Care Unit and were discharged alive from Intensive Care Unit.

	HR[a]	95%CI	p-value
Sex			
Male	1	–	–
Female	0.84	0.70–1.01	0.0524
Age			
18–45 years	1		
45–64 years	4.72	2.18–10.23	<0.0001
65–79 years	10.23	4.79–21.84	<0.0001
≥80 years	18.30	8.49–39.45	<0.0001
Charlson comorbidiy score (continuous)	1.22	1.17–1.27	<0.0001
Days in ICU			
4-7	1	–	–
8-14	1.50	1.21–1.87	0.0002
>14	1.90	1.49–2.43	<0.0001
Overall length of stay			
4–28 days	1	–	–
>28 days	0.76	0.64–0.92	0.0061
Mechanical ventilation			
No	1	–	–
Yes	1.13	0.93–1.38	0.2233
Year of admission (continuous)	0.96	0.93–0.99	0.0174

Abbreviations: HR = hazard ratio; 95%CI = 95% confidence interval; ICU = intensive care unit.
[a]Analysis adjusted for all the factors included in the Table and for AHRQ-CCS diagnosis groups.

with long ICU stay is at higher risk for long-term complications than the total ICU population, since they are more likely to suffer from more severe illnesses. This is the likely reason why the one-year post-ICU discharge mortality in our study was higher than that reported by Soliman et al., who included in his study all ICU-patients, regardless of length of stay [12].

On the other hand, in our cohort, one-year post-ICU discharge mortality (29.6%) was similar to that observed in a similar study of Steenbergen et al. in Amsterdam, where a large proportion of deaths occurred in the first few weeks after ICU discharge in patients who received ICU treatment for more than72 h [7]. Another multicenter study reported that 6–25% of patients discharged alive from the ICU die before hospital discharge [13] and indicated the implementation of decisions to withhold or withdraw life-sustaining treatments during the ICU stay as the most powerful predictor of post-ICU mortality. Appropriateness of triage before ICU admission, ICU case-mix, availability of appropriate post-ICU care and ICU bed availability are factors that could influence the decision to discharge a patient from the ICU and the following outcome [7]. Among the causes of in–hospital early mortality after ICU discharge, we should consider the significant lower patient/nurse and doctor ratio and technological support differences existing between ICUs and general ward. A recent European multicenter study showed that in hospitals with Intermediate Care Units, characterized by lower level of nursing staff and costs than the ICU but higher than the general wards, in-hospital mortality of ICU patients is lower [9]. Accordingly, the potential advantages of establishing and strengthening semi-intensive critical care and early rehabilitation in the ICU should be considered.

Our results are similar to those reported by Steenbergen et al. [7], where increased age and comorbidity were significantly associated with increased one-year mortality. This finding underlines the importance of a careful assessment of patients at ICU admission, also recognizing those who are more likely to have a worse prognosis. Several severity of illness scores are proposed to guide decisions in critical care treatment [14], although clinical judgment and shared decisions with the patients' families remain of crucial importance.

The importance of a careful assessment of the appropriateness of ICU admission based on patients' characteristics is stressed also by the higher in-hospital mortality that we observed as compared with the Dutch data [7]: 32% vs 26%. The excess mortality we observed was due to ICU deaths (22.9% vs 14%). Differences in ICU mortality may either depend on quality of ICU care or on baseline characteristics of patients admitted to the ICU, including severity of illness, age, and comorbidities. The Dutch study does not report such information on all ICU patients, therefore we could not compare our overall case-mix with theirs. Nonetheless, in our hospital, a critical review of ICU deaths is needed.

Among ICU survivors, survival differed according to the underlying cause of hospitalization. We observed higher one-year mortality for neoplastic patients and lower mortality for those hospitalized for traumatic causes, who generally are healthy subjects, apart for the injury. Compared with a German study [15], we observed better one-year post-ICU survival for both sepsis and pneumonia.

The cause of hospitalization also influenced the distribution of in-hospital post-ICU mortality. For example, the number of in-hospital deaths was equal to or greater than those occurring after

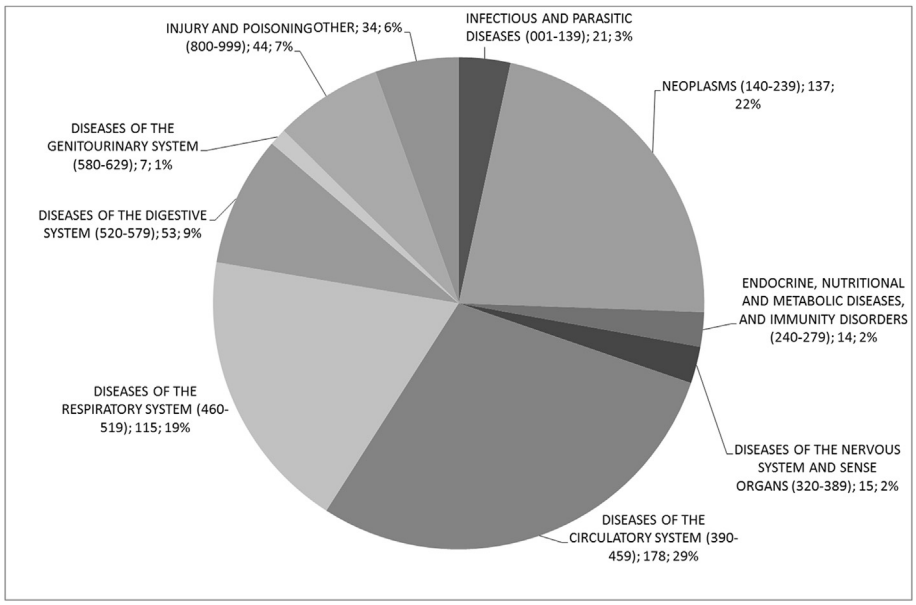

Fig. 3. Causes of all deaths in patients who died within 365 days from discharge from the Intensive Care Unit of the University Hospital of Udine, Italy, from 2006 to 2015, who spent more than72 h in Intensive Care Unit.

hospital-discharge in most cardiovascular conditions, septicemia, shock, coma and brain damage, and hip fracture; the opposite was observed in patients with cancer. These findings also provide useful information for tailoring post-ICU treatment and care.

Patient's age was associated with survival. In fact, the HR of one-year post-ICU mortality among patients ≥80 years of age was almost 20 times greater than that of young adults. Nonetheless, more than half of the subjects in the oldest age subgroup were still alive one year after ICU discharge.

Another important finding of our study is that, adjusting for potential confounders, one-year post-ICU mortality significantly decreased from 2006 to 2015, showing a 4% reduction for each year. This improvement in survival may be due to an improvement in either ICU treatment, or hospital care after ICU discharge, or post-hospital discharge care and rehabilitation or a combination of all.

Survival alone, however, is not sufficient to measure a patient's outcome. In fact, experts recommend also assessing quality of life, using standard validated instruments [3]. This type of research has been conducted in various countries [6,12,15–19]. More and more attention is being devoted to the long-term functioning capacity and quality of life of the ICU survivors. Recently, a post-intensive care syndrome has been described, as a variable combination of cognitive, psychological, and physical signs and symptoms [20] which can affect not only patients but also their families.

4.1. Limitations

Results of this study should be considered in the light of possible limitations. The first limitation is related to the quality of the administrative data we used as source of information. In fact, the use of the main hospital discharge diagnoses to stratify patients might have determined some misclassification in case of poor quality of either diagnosis recording or coding. In addition, the restriction of the analyses to a single hospital limits generalizability of our results to other national and international settings.

4.2. Conclusions

We provided the first analysis of one-year survival of patients with ICU stay in a large Italian hospital. Other long-term outcomes, however, have not yet been investigated in Italy. Prospective studies with periodic active follow-up of ICU survivors are needed as a first step towards awareness that the issue of critical illness does not end with ICU discharge.

Declarations of interest

None.

Funding source

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tacc.2018.07.011.

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