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Comorbidities, Aging and Outcome in ICU

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ABSTRACT

BACKGROUND AND AIMS: We analysed renal, pulmonary, cardiac and hepatic comorbidities in the adult population of Italian ICUs. Our aim was to establish which comorbidity would most affect the outcome of patients admitted to Italian ICUs. The secondary aim was to investigate the role of aging on outcome. **SUBJECT AND METHODS:** In this cross-sectional study we retrospectively enrolled 218,572 patients from179 Italian ICUs from 2011 to 2014, using data available within the Prosafe project database of the GiViTI network. Four comorbidity groups emerged: AKI (renal), COPD (pulmonary), NYHA (heart), PLIVER (hepatic). Each group was drawn from different age-classes. **RESULTS:** The primary outcome was age-specific mortality rates in each comorbidity group**.** Secondary outcome: Incidence rate ratio (IRR) and expected mortality in each comorbidity group. Renal disease represented the main comorbidity in the ICU population. The age-adjusted mortality rates showed the highest mortality rate in the NYHA class. Small difference emerged between NYHA and PLIVER. The IRR, considered as a "predicted" mortality measure, showed PLIVER had a higher predicted mortality rate than the cardiac one (NYHA). In the >75 years of age patients, IRR increased by 50%-55% from the baseline values for PLIVER and NYHA comorbidities, while it rose by 130% and 110% in the COPD and AKI groups, respectively. **CONCLUSIONS:** Cardiac and hepatic comorbidities had the highest ICU mortality. Hepatic disease is associated with a very high sneaky potential also for predicted risk of death. Age should be considered a dependent death risk factor for the comorbidities chosen. Aging impacted markedly on the outcome of elderly patients, particularly if they were pulmonary or renal patients.

INTRODUCTION

In recent years, the number of elderly patients admitted to intensive care units (ICUs) has increased globally.[1] Ageing is characterized by gradual deterioration of functional reserves, comorbidities, disability and functional impairment with reduced independence and autonomy, all of which influence prognoses.[2,3] Many studies focusing on elderly patients in Western countries have evaluated outcomes after their ICU admissions.[4]

In the wards, we manage every patient according to best clinical practice. Since age is often considered as an independent predictive factor of mortality, the elderly are consequently assessed as being at higher risk of death.[5,6] Still it is crucial to pay attention to other features that could strongly influence outcome.[7] Due to the fact that comorbidities act as dependent or independent predictive factors of death, each disease have a different impact on the outcome. Thus, admitting elderly patients to the ICU (or hospital) needs appropriate evaluation of the risk of death, including not only age-related but also comorbidity-related factors, specifically focusing on the comorbidity type.

The aim of this study was to establish which comorbidity would most affect the outcome of patients admitted to Italian ICUs.

The secondary aim was to investigate the role of aging on the outcome of patients with selected comorbidities.

METHODS

1. The GiViTI network and the Prosafe project

Data regarding patients admitted to Italian ICUs were obtained from the GiViTI (*Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva,* Italian Group for the Evaluation of Interventions in Intensive Care) network database.[8]

The GiViTI network, one of the largest ICU research groups in the world, includes most of the Italian ICUs. From its beginning, the GiViTI promoted and implemented a series of research projects with the purpose to describe, analyse and improve the quality of care in Italian ICUs.

"Margherita Prosafe" is one of these research projects.[9,10] Prosafe provides ICUs with a method to measure their own performance continuously, easily, rigorously and confidently. The aims of the project are to standardize data about diagnostic and therapeutic procedures that hospitalised patients undergo, to analyse activity in terms of clinical results derived from the activity and use of resources, and to collect case series for research needs and/or ordinary management of the clinical department. The program's structure integrates basic and specific data collections from different research topics, some of which are still being implemented in order to best describe ICU patients.

In response to a formal application in accordance with the Technical and Scientific Committee requisites, the GiViTI Coordination Centre, which is located in the Clinical Epidemiology Laboratory, Mario Negri Institute, Ranica (BG), provided us with a report on 218,572 adult patients who had been admitted to Italian ICUs from 2011 to 2014, and whose data were collected within the Prosafe project framework.[10] The protocol concerning the data collection was submitted to the Institutional Review Board of the Hospital "Santa Maria della Misericordia" in Perugia that, given the observational and retrospective nature of the study, in accordance with Italian law, waived the need for a formal approval.

2. Description of the study's population

Enrolled patients were drawn from the GiViTI database. Data were collected in the framework of Prosafe software[10] by each ICU, and then extracted by means of a specific analyser .[11]

We evaluated 218,572 patients from 179 Italian ICUs over 4 years, i.e. 1st January 2011 - 31st December 2014 (2011: 47,986 patients; 2012: 55,130 patients; 2013: 58,041 patients; 2014: 57,415 patients)**.** Data were recorded separately for each year of analysis. The analyses included only Italian ICUs in the Prosafe project which recorded validated data for a period of 4 months or longer. Patients in status 3 (discharged) or 4 (dead) were included. ICU mortality data for each patient were recorded at hospital discharge.

We focused on four main comorbidities which, because of severity, could have a strong impact on mortality and which are taken into account when computing mortality predictive scores like SAPS II and SOFA.[12,13] Patients were subdivided on the basis of major cardiac, hepatic, renal and pulmonary comorbidities at ICU admission (**Figure 1**)**.** We identified 4 groups:[10] AKI Group (renal failure, with creatinine value >3mg/dl), COPD Group (Chronic

Obstructive Pulmonary Disease - COPD - with severe hypoxia or hypercapnia, GOLD stage IV); NYHA Group (heart disease - NYHA 4); PLIVER Group (liver disease with portal hypertension or cirrhosis, Child Pugh C). We also considered a reference class, called the "GENERAL Group" that included the general population admitted to ICUs, regardless of comorbidities.

We divided the 5 groups (4 comorbidity groups plus the total population group) into different age ranges: 17-45 years, 46-65 years, 66-75 years, >75 years.

We calculated age-specific mortality rates, standardized mortality rate, and inter-rate differences.

- Age-specific mortality rates were calculated by dividing deaths by population and multiplying by 1000. The result is the so-called crude death rate (CDR). Crude death rates are age-specific weighted means as they use all population age groups to estimate weights.

- Standard rate for each age-group (by means of direct standardization). Using the method of Preston et al.,[14] mortality rates were standardized by adopting weighted means of the 5 classes as reference standards. Mean and percentile distribution were calculated in each class. Means were used to calculate standardized rates.

- Calculating inter-rate differences. Differences were calculated on the basis of age and mean population. The inter-rate difference was partly due to a difference within the group and partly to a difference in rates.[14] The first part of the difference was obtained by applying the class mean to the observed rates and the second by applying the observed group to the mean rates.

3. Statistical analysis

We performed a regression analysis to calculate the Incidence Rate Ratio (IRR) in the age-stratified groups. A dependent variable, such as mortality, may be controlled by means of standardization by age, i.e. as shown above. In our study, we used Poisson's regression analysis as a valid tool to control this variable. The number of deaths is assumed to have a mean and a variance/standard deviation, which are the product of the number of deaths times exposure time. The mean log is therefore the mortality log times the exposure time log. It was used as reference for the 17-45 year old age group. Regression analysis was performed for

each of the 5 groups (4 comorbidities groups plus the general population group). Significant results were considered for $p<0.01$.

The statistical analysis was performed using STATA software (STATA 14.2, Stata Corp. Ltd, TX, USA).[15]

RESULTS

Prevalence of comorbidities varied according to age**.** In the entire analysis period (2011-2014) and considering all ages together, renal disease was the most prevalent comorbidity (AKI group: 8.92% of the ICUs' adult population, i.e. GENERAL group). It was followed by pulmonary (COPD group: 6.98%), hepatic (PLIVER group: 2.72%) and cardiac (NYHA: 3.33%) comorbidities (**Figure 1**).

Considering the general ICU adult population (of all ages), through a raw data analysis, mortality seemed to be the highest in the AKI group (25.54‰), followed by the COPD group (18.64‰), the PLIVER (9.33‰), and NYHA (8.74‰) groups (**Table 1, Figure 2**).

Adjusted data for the relative weight of each co-morbidity at admission, i.e. crude death rates (CDR), were highest in the NYHA group, followed in descending order by the PLIVER, AKI and COPD groups.

The age-adjusted mortality rates (standardized age-related rates) showed the highest mortality rate in the NYHA class. A small difference emerged between NYHA and PLIVER. AKI and COPD showed the lowest mortality rates.

We analysed inter-rate differences by age and by mean population. We found inter-rate differences were derived from a minimal group composition effect and mainly from a real inter-rate difference. That is to say, the groups were homogeneous for factors other than the disease considered (age and other factors not computed), and the observed differences in death rates were related mainly to the comorbidity composition of each group.

Age-related mortality trends (**Figure 3**) showed differences in the selected comorbidity groups of patients. With reference to ageing, in young patients (less than 45 years old) hepatic disease related mortality (PLIVER) was highest. After the age of 45, cardiac mortality (NYHA) predominated until around 70 years of age. At this age, there was a brief period when hepatic mortality (PLIVER) once more became pre-eminent, and over 75 years

of age, NYHA returned to be the most common cause of death. The third major cause of death was renal disease (AKI), steadily increasing throughout all ages. Mortality trends in older ages tend to converge, reflecting reduced differences among comorbidities in terms of outcome and enhanced effect of age. In fact, the mortality trend in the general population (GENERAL class, in figure 2) was impacted by age rather than by the influence of single comorbidities, thus showing a marked and constant increase with age.

Considering overall comorbidities in all age ranges, the IRR (Incidence Rate Ratio) (here considered as an indirect "predicted" or "expected" mortality measure) showed that liver disease (PLIVER) was associated with a higher predicted mortality rate than the cardiac one (NYHA). IRRs for COPD and AKI followed the same trends of observed mortality rates. Results were significant in each comorbidity group, and in each age range ($p < 0.0001$) (**Table 2**).

In the >75 year old patients IRR was the highest in the PLIVER co-morbidity group, increasing by approximately 50% (from 2.00 to 2.96) with reference to the IRRs of patients of all ages (**Table 3**). All other expected mortalities showed similar values, but with different percentages of increase from the baseline value (patients of all ages). In the COPD co-morbidity group the expected mortality rate rose by almost 130% (from 1.26 to 2.88); in the AKI group it increased by 110% (from 1.34 to 2.84). On the other hand, in the NYHA group expected mortality (2.88) increased by "only" 55 %**.**

DISCUSSION

This retrospective observational study doubtlessly shows that patients with cardiac and hepatic comorbidities had the highest ICU mortality, that is to say these comorbidities could influence outcome even more strongly than severe pulmonary or renal impairment. Most evident were two mortality clusters that emerged with paired comorbidities: cardiac and hepatic *versus* renal and pulmonary.

We speculate on how to explain these higher mortality rates of cardiac and hepatic patients. One might presume that few therapeutic resources are available for cardiac patients with severe heart dysfunction (NYHA class IV) except for palliative care with, for example, an ICD implant.[16] Like patients with cardiac disease, patients with liver disease also have a high mortality rate, perhaps mainly because no effective therapy is available today for liver diseases.[17] Therefore, the patient with heart disease could die because all therapeutic options

have been tried and failed while the patient with liver disease cannot avail himself of any valid therapy. On the other hand, patients with renal or pulmonary disease receive intensive care and very effective support therapies like dialysis and invasive mechanical ventilation,[18] which could justify the observed ICU mortality.

The effect of age on the ICU population was ruled out through previous statistical analyses, and the difference in observed mortality rates for patients with each comorbidity showed that ICU outcomes were linked to disease type and severity rather than to different age-group distributions.

Considering ageing and comorbidity mortality trends (**Figure 3**), we speculate that even if patients with cardiac disease have the highest rate of death due to ageing, mortality rates plateau in the 50 to 70 year old age range, presumably because screening programmes are now being implemented in the population at risk.[19-21] Nevertheless, this benefit should be lost after the age of 70, when cardiac mortality starts to rise again.

At the same age when the cardiac death risk plateaus, patients with hepatic disease become at higher risk of death, maybe due to sudden arrhythmia,[22,23] but possibly to other unknown causes.

Mortality in COPD patients tended to increase after 55 years of age, perhaps because other comorbidities developed as the respiratory system's functions decline.[24] The constant increase in death risk in patients with end-stage renal failure probably reflects the ineffectiveness of supportive therapy (renal replacement techniques) in reducing mortality[25-28] and, moreover, an increase in risk factors.[29]

Special reflection should be made regarding young patients. Interestingly, the young patient affected by one of the four chosen comorbidities appears to have higher mortality risk compared to that of the general population at almost every age (we remember that the general population includes mainly people without these comorbidities, with only a small portion of people with comorbidities). For example, people having severe renal failure at the age of 40 means having the same risk of death as a 75 year old man without that comorbidity. In fact, the four selected comorbidities are so aggressive that in young ages their effect on outcome overshadows the same effect of aging on outcome.

On the other hand, in the elderly the effect of ageing on outcome becomes marked and it is supposedly due to the adding up of several diseases (not considered in our analysis) and to an associated para-physiologic impairment on functional systems deputed to homeostasis.

Data analysis indicated age was a dependent death risk factor for the comorbidities considered. Age impacted little on the outcomes in young patients, where it acts as a protective factor (in statistical terms). However, it impacted markedly in the older, and even more in the elderly. In the last life stages the risk of death doubled (100% increase) in the pulmonary and renal patients and increased by half in the hepatic and cardiac ones. Thus, close attention needs to be paid to the elderly with comorbidities like COPD and renal failure which, at least theoretically, constitute powerful risk factors for death.

Another useful suggestion for clinicians regards hepatic comorbidity. Despite its harmful potential, in clinical practice, it is often under-estimated because symptoms and objective signs are less specific.[30] Moreover, physicians often evaluate liver disease as a lower mortality risk than cardiac disease, COPD or renal failure, although the latter could be treated by means of standardized devices, dialysis or mechanical ventilation, while less specific treatments are available for liver disease (plasmapheresis, MARS therapy, etc). Thus, clinicians should pay the same attention to hepatic patient as they do with cardiac NYHA class IV patients. Moreover in medical education, doctors are trained to recognize and treat a patient with cardiac disease immediately but do not always realise that a patient with liver disease may be in the same risk category.

The power of the present study lies in its large scale study population, which may be considered representative of Italian ICUs. Although some sub-groups offer small sample sizes (e.g. the hepatic group), this limitation was overcome by analysing four years of data records. Second, although focus was on elderly people, the study attempts to examine all adult age ranges (paediatrics were excluded) so its results could be considered valid for a large portion of the ICU adult population.

Nevertheless, some limitations of this study should be taken into account. First, this is an observational retrospective study, obviously less powerful than a prospective randomized analysis. Moreover, we analysed aggregate data, so the comorbidity groups often overlap. We speculate on an important portion of the ICU adult population who presented with multiple comorbidities. These classes of patients are expected to have a higher risk of death compared

to single comorbidity patients. Our analysis was not able to explore this issue since the limits of the Prosafe software analyser precluding analyses discriminating between patients with more than one comorbidity. However, it is important to consider the study's findings in the perspective of enlightening the physician to which comorbidity - when present - should be weighted most in the appraisal of patient outcome. Finally, frailty was not assessed as an independent risk factor of death even though frail patients were reported as often not coinciding with the comorbidity-affected patient although frailty is known to influence outcome.[31,32] Future studies are warranted comparing frailty with age and comorbidities so as to assess the impact of each factor in causing death. This could represent a suggestion for including frailty and its assessment in the Prosafe report form hereafter.

Some brief ethical considerations need to be elicited. Although many epidemiological data relate to patient admissions to the ICU,[33-35] little information is available on the quality of care of elderly patients after ICU admission. European data support the hypothesis that more and more patients have access to medical care when they are close to death.[36-38] Thus, resource utilization in elderly patients with high-predicted mortality emerges as a very pertinent issue in intensive care medicine.[39,40] A level of care that is not appropriate for the real survival chances is improper and financially disadvantageous. When admitting patients to the ward or hospital, attention should focus more on patients at high risk of death in order to identify and treat reversible conditions early and prevent end-stage status. On the other hand, starting palliative, rather than intensive, care could be a strategy that might really improve the quality of life, even in end-stage patients.

CONCLUSIONS

Among the recorded comorbidities, the cardiac and hepatic ones had the highest ICU mortality. Hepatic disease is the comorbidity requiring the most attention, as it is associated with a very high sneaky potential for both predicted and observed risk of death. Patients with liver disease should be considered as being at as high a risk of death as NYHA class IV patients.

Furthermore, age should be considered as a dependent death risk factor for these comorbidities. Young patients with one of these comorbidities have a higher mortality than a healthy 75 year old man. Aging impacted markedly on the outcome of elderly patients, where the risk of death rises more than twice in the pulmonary and renal patients and increases by

half in the hepatic and cardiac ones. Physicians should pay close attention to the elderly with comorbidities like COPD and renal failure, which constitute powerful risk factors for death at this age.

Careful assessment of patients with these end-stage kinds of comorbidities becomes important when admitting them to hospital in order to draw up suitable therapeutic flow-charts, fitting their real chance of survival.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

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TABLE LEGEND

Table 1. ICU number of deaths, mortality rates, crude death rates (CDR) and standardized age-related rates

Table 2. Incidence Rate Ratio and Poisson's regression analysis

Table 3. Incidence Rate Ratio increase in elderly patients (age over 75)

TABLES

Table No. 1: ICU number of deaths, mortality rates, crude death rates (CDRs) and standardized age-related rates

Comorbidity group	Deaths (N)	Mortality rate (‰)*	Crude death rate (CDR) (‰)	Standardized age-related mortality rate (‰)
GENERAL	38,130	174.45	174.45	177.48
AKI	5,564	25.45	285.51	270.72
COPD	4,076	18.64	267.08	253.89
NYHA	1,911	8.74	397.13	379.14
PLIVER	2,040	9.33	342.49	357.19

Mortality rate was calculated as ratio between number of deaths and GENERAL population of all ages times 1000, in four-years period. Crude death rates (CDRs) were calculated by dividing deaths by population and multiplying by 1000. Different form mortality rates, crude death rates are "age-specific" and "comorbidity-adjusted"; in the present case all ages are considered together, and reference population in the GENERAL population.

The NYHA group has the highest mortality, followed in descending order by the PLIVER, the AKI, the COPD, and the GENERAL groups.

Once adjusted for age (standardized age-related rates), mortality rates follow the same trends. To note are smaller the differences between NYHA and PLIVER and between AKI e COPD, the latter having much lower mortality rates.

Abbreviations: AKI: severe renal failure, COPD: Chronic Obstructive Pulmonary Disease with severe hypoxia or hypercapnia; NYHA: heart disease NYHA class 4; PLIVER: liver disease with portal hypertension or cirrhosis. GENERAL is the reference class including the general population admitted to ICUs, regardless of comorbidities.

Table No. 2: Incidence Rate Ratio and Poisson's regression analysis

Comorbidity group	IRR	[95% Confidence interval]			P value	Pseudo R2
GENERAL	0.63 *	0.61	-	0.66	<0.0001	0.84
AKI	1.34 *	1.27	-	1.42	<0.0001	0.64
COPD	1.26 *	1.18	-	1.35	<0.0001	0.61
NYHA	1.85 *	1.69	-	2.03	<0.0001	0.66
PLIVER	2.00 *	1.83	-	2.19	<0.0001	0.69

All ages were considered together, using age 17-45 as reference age. *Results were significant for $p < 0.0001$.

The Incidence Rate Ratio (IRR), as a predictive parameter of mortality, showed that patients with liver disease (PLIVER) have a higher expected mortality rate than NYHA. Even if the crude death rate was higher in cardiac patients and NYHA comorbidity is extensively treated, it appears that hepatic disease is associated with the worst outcome.

Note that the GENERAL population group has a lower than 1.00 IRR, because of the sample size includes most of the subjects without the four comorbidities (the general population is mainly healthy, i.e. not comorbidity-affected).

Abbreviations: IRR, Incidence Rate Ratio; AKI: severe renal failure, COPD: Chronic Obstructive Pulmonary Disease with severe hypoxia or hypercapnia; NYHA: heart disease NYHA class 4; PLIVER: liver disease with portal hypertension or cirrhosis. GENERAL is the reference class including the general population admitted to ICUs, regardless of comorbidities.

Table No. 3: Incidence Rate Ratio increase in elderly patients (age over 75)

Comorbidity group	IRR all ages	IRR age >75	Δ increase (%)
AKI	1.34	2.84	**110.93**
COPD	1.26	2.88	**127.63**
NYHA	1.85	2.88	**55.26**
PLIVER	2.00	2.96	**47.95**

The table shows the average Incidence Rate Ratio (IRR) coefficients (all ages together) and the IRRs of elderly patients (>75 years of age) for each kind of comorbidity, and the percentage delta-increase in the IRRs calculated, using mean values, as:

[(IRRs >75y) – (IRRs all ages)] / (IRRs all ages) * 100 .

The IRR increases for the general population (GENERAL class) are not shown.

Although in the elderly expected mortality was higher in hepatic patients (PLIVER) (see also Table 2), the overall pattern indicated a marked trend of increase in comorbidities other than hepatic. The rise was, in fact, greater in the pulmonary-renal comorbidity groups (COPD-AKI) (i.e. expected mortality doubled) rather than in the hepatic-cardiac ones (PLIVER-NYHA).

Abbreviations: IRR, Incidence Rate Ratio; AKI: severe renal failure, COPD: Chronic Obstructive Pulmonary Disease with severe hypoxia or hypercapnia; NYHA: heart disease NYHA class 4; PLIVER: liver disease with portal hypertension or cirrhosis.

FIGURES

Figure 1. Study population

Figure 2. ICU number of deaths according to age

Figure 3. Age-related mortality pattern

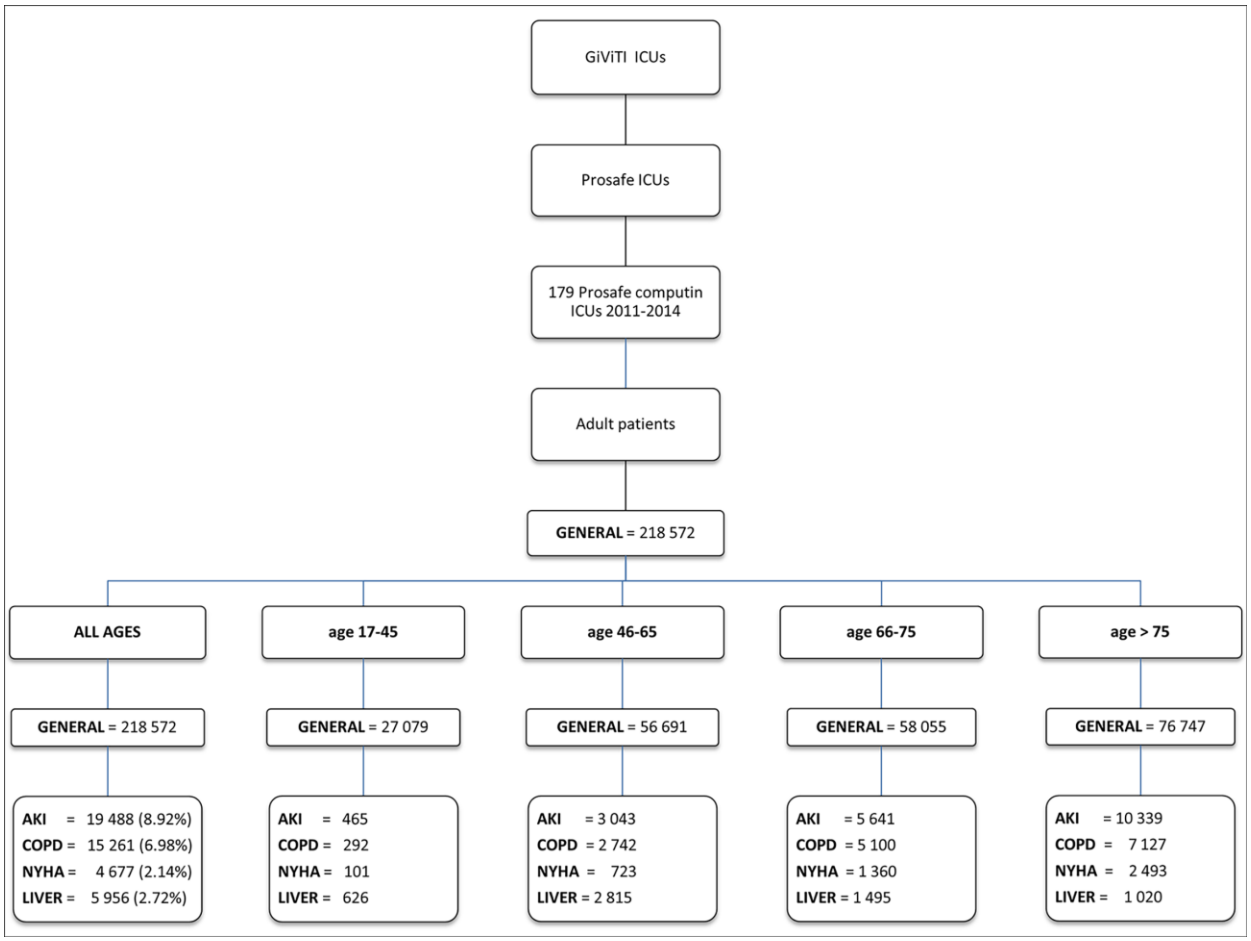

Figure No. 1: Study population

The enrolled Italian ICU population was extracted from the GiViTI network ICUs. We considered the Prosafe computing ICUs in the period 2011-2014 which recorded validated data for a period of 4 months or longer. Patients in status 3 (discharged) or 4 (dead) were included. Data were recorded separately for each year of analysis.

Four age ranges of the adult population (GENERAL group) were chosen. We analyzed four main end-stage comorbidity groups: AKI Group: renal failure, with creatinine value >3mg/dl; COPD Group: chronic obstructive pulmonary disease, COPD GOLD stage IV; NYHA

Group: hearth disease, NYHA class IV; PLIVER Group IV: liver disease with portal hypertension or cirrhosis, Child Pugh C. See text for details. Data are presented as absolute values or percentage of the GENERAL population group.

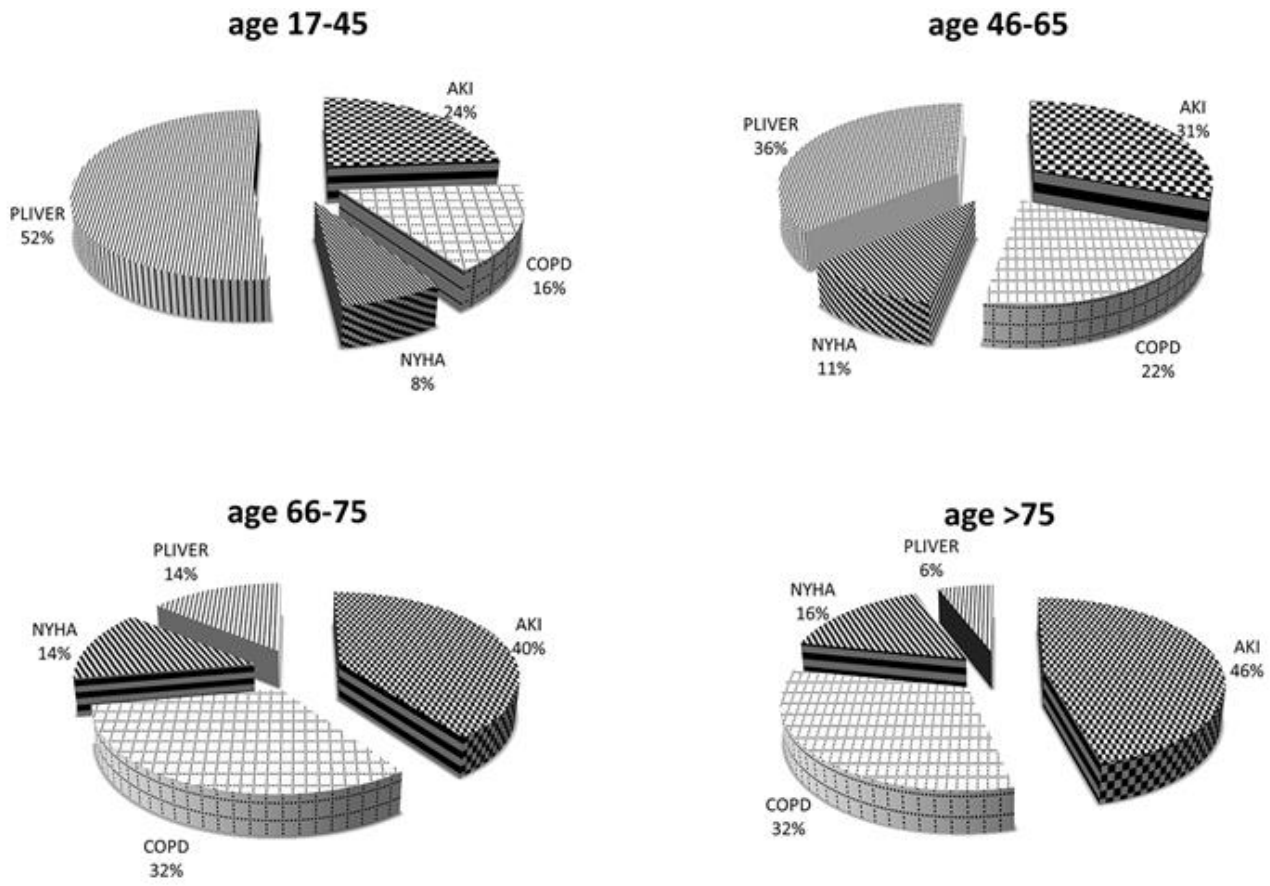

Figure No. 2: ICU number of deaths according to age

Abbreviations: AKI: severe renal failure, COPD: Chronic Obstructive Pulmonary Disease with severe hypoxia or hypercapnia; NYHA: heart disease NYHA class 4; PLIVER: liver disease with portal hypertension or cirrhosis. GENERAL is the reference class including the general population admitted to ICUs, regardless of comorbidities.

Data are presented as the relative number of deaths (%) among patients with comorbidities, according to age ranges.

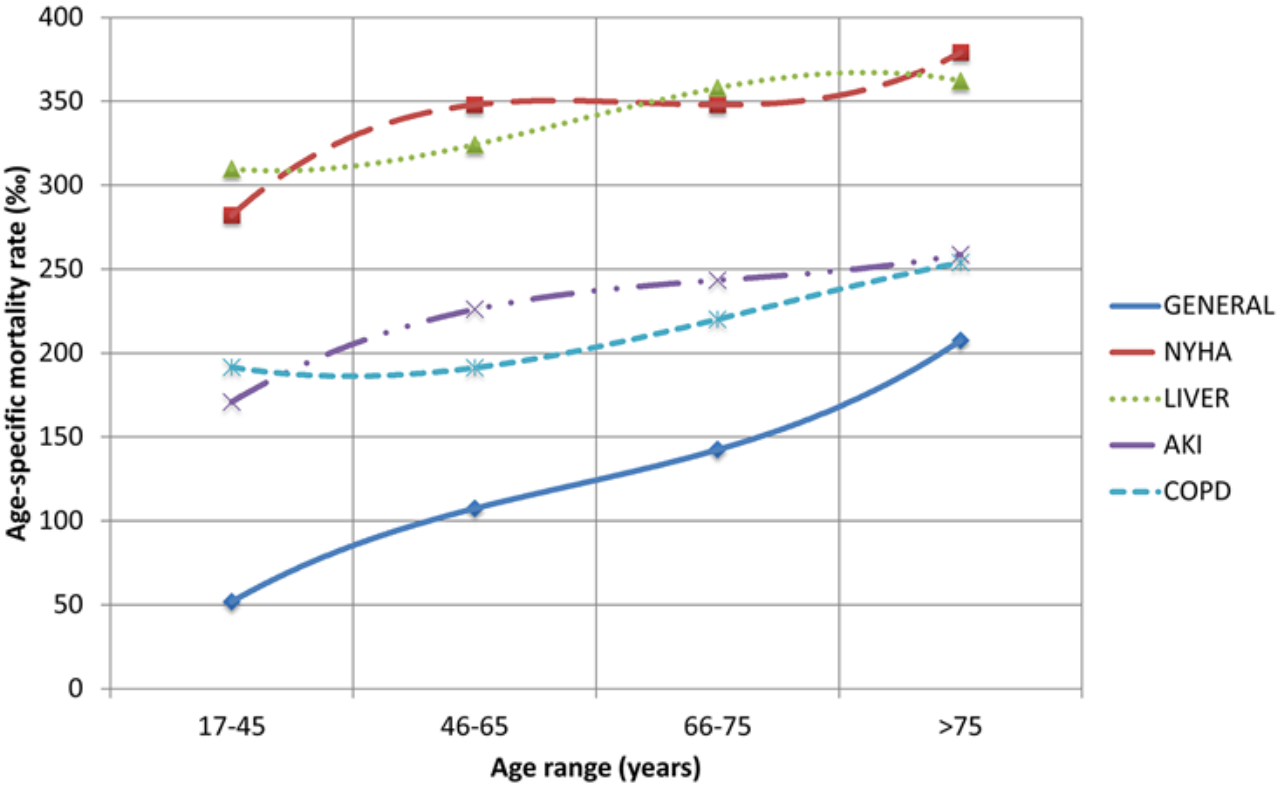

Figure No. 3: Age-related mortality pattern

Abbreviations: ASMR, Age-specific mortality rates; AKI: severe renal failure; COPD: severe Chronic Obstructive Pulmonary Disease; NYHA: heart disease NYHA class 4; PLIVER: end stage liver disease. GENERAL is the reference class including the general population admitted to ICUs, regardless of comorbidities.

The figure illustrates mortality trends in relation to the mean age of the diverse age groups.

Relevant features:

-Two mortality clusters emerged with paired comorbidities: cardiac and hepatic *versus* renal and pulmonary.

-In young patients (under 45 years old), hepatic disease related mortality (PLIVER) was highest. After the age of 45, cardiac mortality (NYHA) predominated until around 70 years of age.

-Renal disease (AKI) mortality steadily increased with age, while the pulmonary one (COPD) started increasing only after 55 years of age.

-Ageing is characterized by the convergence of mortality trends. This reflects reduced differences among comorbidities in terms of outcome and the enhanced effect of age.

-The mortality trend of the general population (GENERAL) was impacted by age rather than by the influence of single comorbidities, thus markedly and constantly increasing with age.