Variations in end-of-life care practices in older critically ill patients with COVID-19 in Europe

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Running Headline: End-of-life care in COVID-19

Abstract

Background

Previous studies reported regional differences in end-of-life care (EoLC) for critically ill patients in Europe.

Objectives

The purpose of this post-hoc analysis of the prospective multi-centre COVIP study was to investigate variations in EoLC practices among older patients in intensive care units during the coronavirus disease 2019 pandemic.

Methods

A total of 3105 critically ill patients aged 70 years and older were enrolled in this study (Central Europe: n=1573; Northern Europe: n=821; Southern Europe: n=711). Generalised estimation equations were used to calculate adjusted odds ratios (aOR) to population averages. Data were adjusted for patient-specific variables (demographic, disease-specific) and health economic data (GDP, health expenditure per capita). The primary outcome was any treatment limitation, and 90-day-mortality was a secondary outcome.

Results

The frequency of the primary endpoint (treatment limitation) was highest in Northern Europe (48%), intermediate in Central Europe (39%), and lowest in Southern Europe (24%). The likelihood for treatment limitations was lower in Southern than in Central Europe (aOR 0.39; 95%CI 0.21-0.73; p=0.004), even after multivariable adjustment, whereas no statistically significant differences were observed between Northern and Central Europe (aOR 0.57; 95%CI 0.27-1.22; p=0.15). After multivariable adjustment, no statistically relevant mortality differences were found between Northern and Central Europe (aOR 1.29; 95%CI 0.80-2.09; p=0.30) or between Southern and Central Europe (aOR 1.07; 95%CI 0.66-1.73; p=0.78).

Conclusion

This study shows a north-to-south gradient in rates of treatment limitation in Europe, highlighting the heterogeneity of EoLC practices across countries. However, mortality rates were not affected by these results.

Keywords: critical care, COVID-19, frail elderly, resuscitation orders, public health systems research

Introduction

Many individuals receive prolonged and invasive intensive care treatments at the end of their lives. The definition of treatment goals represents an important component in the treatment of critically ill patients, and therapy limitations need to be discussed when specific therapies become futile and/or death inevitable. These decisions can be difficult, and practices vary by physician, hospital, and country. A general principle of medicine is to do no harm. However, there is a fine line between where modern intensive care encounters biological limits, especially in very old and severely ill patients. Finally and most importantly, the preservation of an individual's dignity and autonomy should always come first, and protracted suffering should be avoided. Avidan et al. recently confirmed in the Ethicus-2 study that end-of-life practices are subject to regional variations [1]. These differences are observed worldwide, which is presumably due to social, religious, and/or legal reasons [1,2]. However, a deeper understanding of these regional differences could contribute to a better mutual understanding and help decision makers adjust guidelines and organisational frameworks accordingly.

However, the data from Avidan et al. predate the COVID-19 era [1]. The COVID-19 pandemic put immense pressure on Europe's heterogenous but highly developed health-care systems, and in particular on intensive care units [3]. Even before COVID-19, older critically ill patients posed not only a medical but also an ethical challenge, as the added value of intensive care for older patients and especially octogenarians is the subject of ongoing debate [4–7]. In addition to a clinical assessment and a structured evaluation of the severity of an acute illness, the evaluation of frailty—which reflects the functional capacity of patients prior to the acute illness—has also been proven to be helpful in increasingly ageing societies [8]. In particular, the Clinical Frailty Scale (CFS), among others, has been confirmed by our group as an independent predictor of mortality in critically ill older patients [2,9,10].

The aim of this study was to investigate regional variations within Europe with regards to the use of treatment limitations in older (≥70 years) critically ill patients with COVID-19. Furthermore, baseline characteristics and mortality between three distinct European regions were compared.

Materials and Methods

COVIP

COVIP (COVID-19 in very old intensive care patients) is a multi-centre investigation which is part of the Very Old Intensive Care Patients (VIP) project (www.vipstudy.org). The study has been endorsed by the European Society of Intensive Care Medicine (ESICM). COVIP was registered on ClinicalTrials.gov (NCT04321265). The COVIP study adhered to the European Union General Data Privacy Regulation (GDPR) directive. As in the previous VIP studies, the national coordinators recruited the intensive care units (ICU), coordinated national and local ethical permissions, and supervised patient recruitment at the national level [2,10]. The COVIP study protocol is available at https://vipstudy.org/covip-study/.

Study participants and general information

In this post-hoc analysis of the prospective COVIP study, all patients aged 70 years and older admitted to the ICU with confirmed COVID-19 by means of (polymerase chain reaction/PCR) with complete data on the primary endpoint (any treatment limitation) were included. All patients admitted between 19 March 2020 and 4 February 2021 were included. Data collection started on ICU admission. The admission day was defined as day one, and all consecutive days were numbered sequentially from the admission date. For each patient, baseline characteristics (including age, sex, main reason for admission, and frailty) and management strategies (including use of renal replacement therapy [RRT], mechanical ventilation [MV], non-invasive ventilation [NIV], and use of vasoactive drugs) were documented. Also, any treatment limitations (treatment withheld or withdrawn) were documented. Patients were defined as belonging to Central Europe (Austria, Belgium, France, Germany, Poland, Switzerland), Northern Europe (Denmark, Ireland, Netherlands, Norway, United Kingdom) or Southern Europe (Greece, Israel, Italy, Portugal, Romania, Spain). In this respect, we have used a country classification similar to the Ethicus-2 study [11]. 90-day follow-up was obtained by means of telephone interviews. The primary endpoint of this study was any treatment limitation, and the secondary endpoints were ICU-, 30- and 90-day-mortality and rates withholding and withdrawing treatment. Frailty was assessed by the Clinical Frailty Score (CFS), and the respective visual and simple descriptions were used with permission [8,12]. The gross domestic product (GDP) per capita for 2019 in US-$ was retrieved from the International Money Fund (IMF) [13], the human development index (HDI) from the United Nations Development Program (UNDP) [14], and the total (compulsory, out-of-pocket, voluntary) amount of health spending per capita in US-$ in 2019 from the Organisation for Economic Co-operation and Development (OECD) [15]. A general review of the literature prior to conducting the study was conducted, and the corresponding search terms can be found in Supplement 1.

Each study site obtained institutional research ethics board (IRB) approval. Many countries could recruit patients without informed consent while others had to collect informed consent as ethical consent practices vary across Europe.

Statistical analysis

The primary exposure was belonging to one of the three European regions. Central Europe was chosen as the reference category and compared to either Northern or Southern Europe. Missing data (including loss to follow-up) were addressed by listwise deletion. The data are likely to be clustered at an ICU level. To compensate for possible confounders, a multilevel regression analysis was used. As health economic data do not vary within a given cluster (as patients in one ICU belong to one country), generalised estimation equations (GEE) with robust standard errors were used to produce population average odds ratios for the binary endpoints treatment limitation and mortality. Adjusted odds ratios (aORs) and respective 95% confidence intervals (95%CI) were obtained. We fitted a multilevel linear regression model to evaluate the association of the primary exposure with the length of ICU stay as dependent variable and obtained regression coefficients and respective 95%CI. The regression analyses were conducted using only robust estimators of the standard errors and not in the sense of robustness against violations of normality assumptions as for the methods (e.g., Mann-Whitney tests) used for the univariate analyses. Model-1 includes only the ICU as a panel. Model-2 includes patient-specific factors (sex, age per year, sequential organ failure assessment (SOFA) score per point, frailty score per CFS point). Model-3 adds the number of ICU beds per 100,000 inhabitants. Model-4 includes the health economic data (HDI). Model-5 adds the treatment limitations (treatment withdrawal or withholding) and calculates mortality and the ICU length of stay. Sensitivity analyses stratifying treatment limitation were done. Continous data are given as median ± interquartile range (IQR) and compared using the Mann-Whitney U test or given as mean ± standard deviation and compared using the Student's t-test. Categorical data are given as numbers (percentages) and compared using the chi-square test. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. Stata/IC 17 (Stata Statistical Software: Release 17. StataCorp LLC, College Station, Texas, United States of America) was used for all statistical analyses.

Results

Baseline demographics in Central versus Northern and Southern Europe

In total, 3105 older (≥70 years) critically ill patients were included in this study—1573 in Central Europe, 821 in Northern and 711 in Southern. The baseline characteristics are given in Table 1. No differences in sex distribution within regions were found. Patients in Central Europe (23%) were more frequently older than 80 years old compared to Northern (14%) and Southern Europe (16%) (p<0.001). Likewise, patients in Central Europe (19%) were more likely to be frail and suffer from cardiovascular comorbidities than those from Northern and Southern Europe (see Table 1). The ICUs included in Central Europe had a higher median number of ICU beds (12) compared to Northern (7) and Southern Europe (10) (p<0.001). The results of the univariate analysis on baseline characteristics are shown in Table 1.

Organ support and management

In the univariate analysis, ICU length of stay was significantly longer in Southern Europe (median 21 days) than in Central and Northern Europe (median 15 days each; p<0.001). This finding remained after performing multilevel linear regression analysis across all five models (see table in Supplement 2). The figure in Supplement 3 shows the median length of stay in the groups with and without treatment limitations according to the three regions. Intubation and mechanical ventilation rates were highest in Southern Europe (85%), followed by Central (69%) and Northern (67%) (p<0.001). Likewise, tracheostomy rates were highest in Southern Europe (31%) and lowest in Central (16%) (p<0.001). By contrast, the use of renal replacement therapy (RRT) was most common in Central Europe (18%), and least common in Northern (12%) (p<0.001). The results on management strategies of the univariate analysis are shown in Table 2.

Treatment limitation analysis

The frequency of the primary endpoint (any treatment limitation) was highest in Northern Europe (48%), lowest in Southern (24%) and intermediate in Central (39%; p<0.001). A decreasing incidence of withholding and withdrawing treatment was observed from north to south (see Table 2). Table 3 shows the multivariable regression analyses. The odds for any treatment limitation were lower in Southern Europe compared to Central (aOR 0.39 95%CI 0.21-0.73; p=0.004) even after adjustment for patient-specific characteristics, ICU beds per 100,000 population, and the HDI. No statistically significant differences were observed between Northern and Central Europe (reference category) (aOR 0.57 95%CI 0.27-1.22; p=0.15). The rates of withholding and withdrawing treatment showed a similar pattern, with the highest rates in Northern Europe and the lowest rates in Southern Europe (see Table 2).

Mortality analysis

ICU mortality was highest in Southern Europe (51%), and lower in Northern (43%) and Central Eruope (44%) (p=0.003). The 30-day mortality rate was similar in the three regions (see Table 2). In univariate analysis, 90-day mortality was highest in Southern Europe (62%) and similar in Central (56%) and Northern Europe (56%) (p=0.019). After adjustment for patient-specific characteristics, ICU beds per 100,000 population and HDI, no mortality differences were found between Northern Europe compared to Central Europe (aOR 1.29 95%CI 0.80-2.09; p=0.30), and Southern Europe compared to Central Europe (aOR 1.07; 95%CI 0.66-1.73; p=0.78). Figure 1 shows a comparison of the survival probability of patients from the three regions.

Sensitivity analyses

In sensitivity analyses comparing treatment limitations between European regions, there was a consistent trend towards lower odds for any treatment limitation in Southern Europe versus Central Europe (see Forest plot in Figure 2) and higher odds for any treatment limitation in Northern Europe versus Central Europe (see Forest plot in Figure 3).

Discussion

In this study, differences in the incidence of treatment limitations among critically ill older (≥70 years) patients in three European regions were investigated. A north-south divide was observed: Treatment limitations were more common in Northern Europe than in Southern Europe. However, the use of treatment limitations does not appear to translate into a mortality difference after correcting for various confounders.

In general, treatment goals should always be set for critically ill patients. If feasible, the benefits versus the risks of treatment should be considered for every patient. Ideally, a decision to withhold invasive intensive care measures should be made prior to ICU admission, yet in reality these expectations are not always met [16]. In addition to the declared will of an individual (if available and realistic) and the current state of the acute illness, the patient's past medical history (including previous illnesses, frailty, duration of inpatient stay, and previous hospitalisations) should also be taken into consideration for any treatment decision [16]. Furthermore, functional and nutritional status are of paramount importance. Additionally, it is essential to distinguish between withholding or withdrawal of treatment, as well as to note that limitations of treatment (especially withholding of ICU care) are not necessarily associated with an increased short-term mortality [17].

The fact that a north-south divide in EoLC practices exists in Europe is a well-known phenomenon. Sprung et al. showed that the number of patients with treatment limitations put in place is gradually increasing. This could be for a number of reasons. It is certainly not only due to the ageing population of critically ill patients, often with significant comorbidities, but also due to increased public awareness, improved diagnostics, and the growing body of guidelines and treatment recommendations, which allow for a more structured approach in the daily intensive care routine [18,19].

Baseline risk distribution

This study observed discrete variations in patient-specific differences between the three European regions studied, which may reflect regional variations in ICU admission policies [20–22]. In addition to the known increased number of critical care beds in Central Europe, a higher proportion of patients over 80 years of age and individuals with previously known frailty were found in this region [23]. Nevertheless, a significant—though not vast—difference was observed between the three regions with regards to median patient age and the severity of the acute ilness. This also fits well with one of our preliminary studies, in which we showed that countries with different health-care systems admitted patients with different characteristics to their local intensive care units [24]. In addition to the expected difference in GDP between Northern and Southern Europe, there is also a higher level of health spending per capita in Central Europe. Whether the rate of admission of older and more frail patients is a "phenomenon of prosperity" or due to cultural differences can only be speculated. There may be a higher rate of time-limited ICU trials for older patients in Central Europe or a more liberal ICU admission policy as a result of the larger number of ICU beds available per capita; however, that is out of the scope of the present study.

Organ support and management

Furthermore, evidence of variations in intensive care management practices between different regions was found. For example, the rate of mechanically ventilated patients was significantly higher in Southern Europe, translating into a higher proportion of tracheostomies performed. The number of patients who required circulatory support with vasopressors was also higher in Southern Europe. This is particularly interesting given the relatively similar median SOFA score, and may reflect different regional treatment strategies. When treating COVID-19, the early or late use of mechanical ventilation—which allows the application of lung-protective ventilation—and the optimal timing for tracheostomy are the subject of ongoing scientific and clinical debate [25,26]. As is well known, Italy, Spain, Portugal and Israel—all countries in Southern Europe—were hit hard relatively early in the COVID-19 pandemic, and this may have affected how treatment was delivered. Especially in severely affected countries, conventional ICU measures such as non-invasive ventilation (NIV) were often performed on normal wards during times of surge, whereas invasive mechanical ventilation generally remained within the intensive care domain [27]. This could have indirectly contributed to the higher numbers of intubated patients on mechanical ventilation in Southern Europe. Finally, given the similar disease severity described above, a different approach to time limits of NIV-trials and variations in intubation criteria must be considered.

Treatment limitation analysis

The reasons for or against treatment limitations may be due to a patient's personal preference, general ethical/intensive care considerations, and local ICU admission policies. Inherent factors in the health system—such as the training and education of clinicians, existing guidelines, or the weight given to the wishes of the patient's family—may also influence the likelihood of a treatment [18]. In the Ethicus-2 study, it was suggested that the similar observed differences within Europe could also be an expression of changing practices over time, and that changes are implemented more quickly in Northern Europe [28]. However, given the current data, this seems unlikely as the observed differences seen now in 2020 and 2021 show a similar pattern to those seen in the Ethicus-2 study conducted in 2015 and 2016. We therefore believe that the differences observed—now repeatedly and reproducibly—are more structural in nature, although the exact causes remain unclear.

Outcome analysis

Interestingly, the different rates of treatment limitations did not lead to a major difference in regional 90-day mortality rates of critically ill older patients with COVID-19. Ultimately, one can only speculate about the reasons for this finding. A slightly higher proportion of patients over 80 years of age and patients with cardiovascular comorbidities was observed in Central Europe compared with Northern and Southern Europe. Individual treatment strategies also varied—which may be due to different structures of care, but on the other hand could be due to the stress put on intensive care units during surge. Another influencing factor could be the differences in ICU bed numbers, as mentioned previously. Systems with a larger pre-existing ICU bed base are more likely to be able to compensate quickly in times of crisis compared with systems in which new capacity must be created. There may also be differences in terms of staffing-patient ratios. Also, different ICU capacities may imply different up- and down-stream structures (intermediate care or monitoring areas on normal wards). Accordingly, patients with non-invasive ventilation may be admitted to an ICU in some settings and may be cared for on a monitored normal ward in other systems. Thus, in our collective, more patients in Central and Northern Europe received non-invasive ventilation, whereas more individuals in Southern Europe required invasive ventilation. Another interesting finding is that ICU length of stay varied significantly between regions, with the longest lengths of stay in Southern Europe. This is noteworthy, as the rate of treatment limitations was lower there, but there was no statistically significant difference in terms of mortality. It must be taken into account that infrastructure and management vary regionally, and not all details on local structures of care are available in our study. Nevertheless, considering these findings, the structured use of treatment limitations may be useful—especially in times of overcrowding in ICUs in the context of the pandemic—if a possibly longer invasive treatment does not result in a survival advantage for the affected patients. Because the secondary endpoints of 30- and 90-day mortality are not available for all patients, a selection or reporting bias may also exist. This study regardless shows that the different systems had comparable results due to the large amount of time and work invested during the pandemic. In general, a multinational comparison is difficult due to the significantly different health-care systems and ICU bed capacities (as well as subsequent care structures) in the various countries of the three European regions. Nevertheless, the multivariable analysis corrected for all of these factors, which was intended to achieve a balanced comparison across regions.

Conclusion

We conclude that rates of treatment limitations in older patients during the COVID-19 pandemic period in Europe show a north to south gradient. When performing such evaluations, different health-care systems, patient characteristics, and local treatment strategies must be considered. Interestingly, this did not lead to significant differences in mortality rates in a multivariable analysis.

Limitations

One limitation is that we do not know the exact timing of when a treatment limitation was pronounced. We also do not have detailed information on how a "treatment withhold" was defined in an individual case, and it would likely not be possible to evaluate this uniformly for such a large cohort. Unfortunately, we also do not have information on whether patients were transferred to intermediate care units or elsewhere after a treatment limitation was imposed. Further limitations of this study—besides its unblinded design—are the lack of knowledge about the functional outcome, and the problem of a potential self-fulfilling prophecy as always with treatment limitations. Also, in addition to a comparison group with younger patients, a long-term outcome would be interesting because of the often-protracted hospital stay in severe COVID-19 infections. Although it is difficult to generalize qualitative data such as treatment limitations, we think that our study provides useful data for health-care providers and decision makers due to the large number of participants and good patient characterization.

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The map in the Graphical Abstract was generated using https://mapchart.net/ (licensed under a Creative Commons Attribution-ShareAlike 4.0 International License). No (industry) sponsorship has been received for this investigator-initiated study.

Data sharing:

All data relevant for this study will be given by the authors upon specific request without restriction.

Author contributions:

Conceptualization: BW, HF, MJ, DWL, BG, CJ.
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Formal analysis: BW.
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Conflict of Interest:

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Figure legends

Figure 1: Kaplan-Meier curve depicting survival (with 95% CI) of patients in Northern Europe (red) and Central Europe (blue) and Southern Europe (green). *Abbreviations: CI: confidence interval;*

Figure 2: Sensitivity analyses stratifying any treatment limitations in subgroups for patient-specific characteristics using generalised estimation equations (GEE) producing population average odds ratios. The depicted aORs from model-1 include only the ICU as panel. *Abbreviations: aOR: adjusted odds ratio; ICU: intensive care unit;*

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Figure Supplement 3: Median length of stay in patients with no treatment limitation versus individuals with any treatment limitation. *Abbreviations: ICU: intensive care unit; LOS: length of stay;*

	Central Europe (n=1,573)	**Northern Europe** (n=821)	**South** (
Patient-specific variables			
Sex			
Male - n (%)	1,117 (71)	594 (72)	4
Female - n (%)	456 (29)	227 (28)	2
Age at admission – yrs.	76 (5)	75 (4)	
Age categories			
Age <80 years – n (%)	1,211 (77)	703 (86)	5
Age >79 years – n (%)	362 (23)	118 (14)	1
BMI – kg/m^2	28 (5)	28 (5)	
Comorbidities			
Arterial hypertension – n (%)	1,084 (69)	467 (57)	5
Diabetes (any type) – n (%)	558 (36)	240 (29)	2
Ischemic heart disease – n (%)	379 (24)	194 (24)	1
Chronic heart failure – n (%)	237 (15)	122 (15)	8

Pulmonary comorbidity – n (%)	359 (23)	206 (25)	1
Renal insufficiency – n (%)	285 (18)	118 (14)	9
Frailty			
Clinical Frailty Scale Score – pts.	3 (2)	3 (1)	
SOFA score on admission – pts.	6 (3)	5 (3)	
Frailty categories			
Fit – n (%)	941 (60)	507 (62)	4
Vulnerable – n (%)	253 (16)	114 (14)	
Frail – n (%)	288 (18)	125 (15)	8
Frailty category unavailable – n (%)	91 (6)	75 (9)	
Region specific variables			
ICU beds per 100,000 population – no	12 (12-16)	7 (6-7)	1
ICU beds categories			
<10 ICU beds per 100K – n (%)	134 (9)	821 (100)	6
≥10 ICU beds per 100K – n (%)	1,439 (91)	0 (0)	
HDI	0.92 (0.03)	0.94 (0.01)	0.8
GDP per capita in US - $	41,897 (41,897-46,473)	52,646 (42,379-59,770)	29,993 (2
Health spending per capita in US - $	5,376 (5,376-6,646)	5,568 (4,653-5,765)	3,616 (

Table 1: Baseline characteristics of the cohort. *Abbreviations: BMI: body mass index; GDP: gross domestic product; HDI: human development index; ICU: intensive care unit; SOFA: sequential organ failure assessment;*

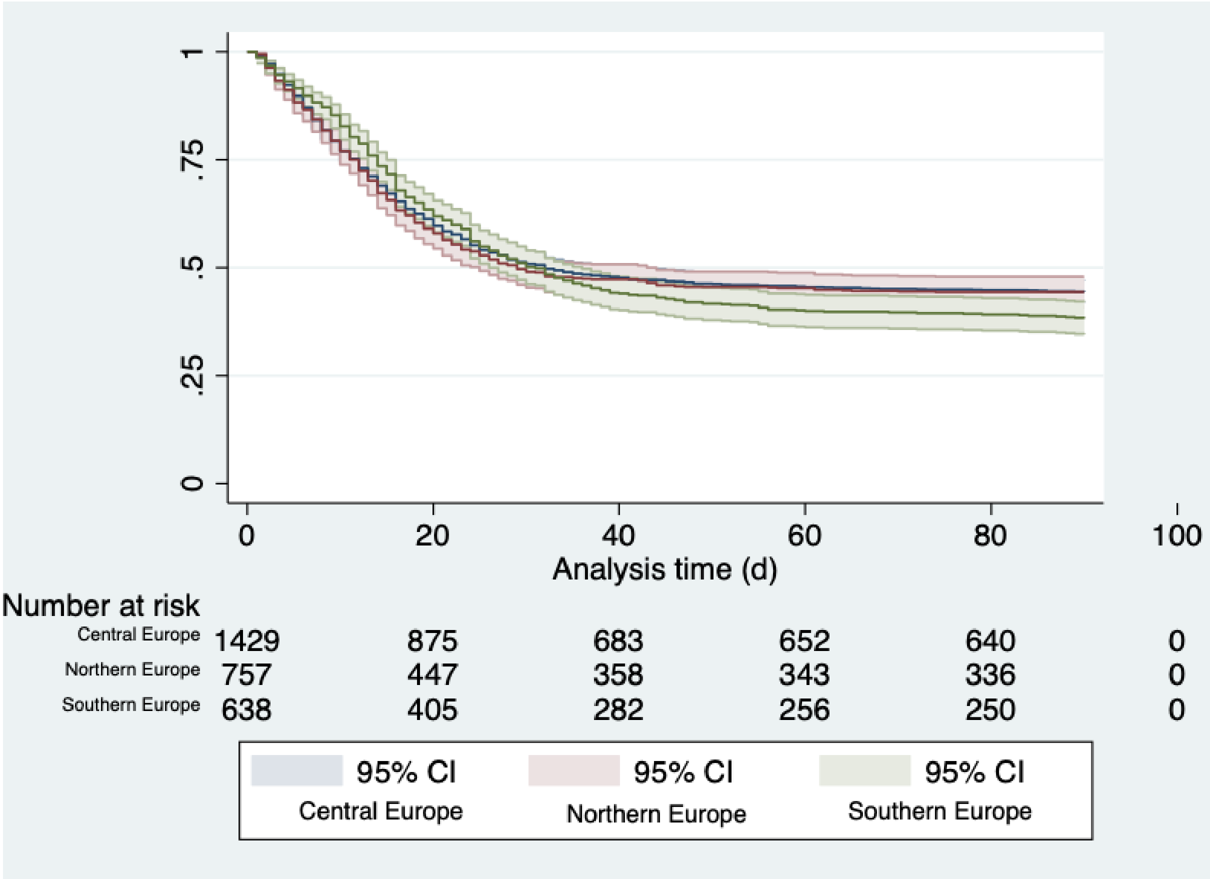
	Central Europe (n=1,573)	Northern Europe (n=821)	Sout
Management strategies			
Non-invasive ventilation – n (%)	419 (27)	220 (27)	
Intubation and mechanical ventilation – n (%)	1,080 (69)	550 (67)	
Tracheostomy – n (%)	254 (16)	163 (20)	
Vasoactive drugs used – n (%)	1,083 (69)	555 (68)	
Renal Replacement Therapy used – n (%)	290 (18)	96 (12)	
ICU length of stay - d	15 (15)	15 (14)	
Primary endpoint			
Any treatment limitation – n (%)	616 (39)	396 (48)	
Secondary endpoints			
Life sustaining care withheld – n (%)	527 (34)	315 (38)	
Life sustaining care withdrawn – n (%)	283 (18)	249 (30)	
ICU mortality – n (%)	692 (44)	349 (43)	
30-day-mortality – n (%)	744 of 1,550 (48)	391 of 798 (49)	341
3-month-mortality – n (%)	804 of 1,436 (56)	421 of 752 (56)	399

Table 2: Management strategies and endpoints. *Abbreviations: ICU: intensive care unit. Note: Due to missing values, 30-day- and 3-month outcomes are calculated only for the set with available outcome value.*

	Primary endpoint (Any treatment limitation)			
	OR	95%CI	p-value	OR
Model-1: ICU as panel variable				

Central Europe	-	-	-	-
Northern Europe	1.53	1.10-2.14	0.01	0.90
Southern Europe	0.56	0.38-0.83	0.004	1.31
Model-2: model-1 + age, sex, SOFA and CFS				
Central Europe	-	-	-	-
Northern Europe	1.63	1.06-2.52	0.03	1.24
Southern Europe	0.48	0.26-0.88	0.02	1.43
Model-3: model-2 + ICU beds per 100,000 population				
Central Europe	-	-	-	-
Northern Europe	0.87	0.52-1.46	0.60	0.84
Southern Europe	0.30	0.15-0.58	<0.001	1.11
Model-4: model-3 + HDI				
Central Europe	-	-	-	-
Northern Europe	0.57	0.27-1.22	0.15	1.29
Southern Europe	0.39	0.21-0.73	0.004	1.07
Model-5: model-4 + any treatment limitation				
Central Europe	N/A	N/A	N/A	-
Northern Europe	N/A	N/A	N/A	1.99
Southern Europe	N/A	N/A	N/A	1.40

Table 3: Generalized estimation equations (GEE) based analysis producing population average odds ratios. Model-1 includes only the ICU as panel. Model-2 includes patient specific factors (sex, age per year, SOFA score per point and frailty score per CFS point). Model-3 adds the amount of ICU beds per 100,000 population. Model-4 includes the HDI. Model-5 adds the rates of any treatment limitations and hence calculated only 90-day-mortality. Adjusted odds ratios (aOR) and respective 95% confidence intervals (95%CI) were obtained. *Abbreviations: CFS: clinical frailty score; CI: confidence interval; HDI: human development index; ICU: intensive care unit; OR: odds ratio; SOFA: sequential organ failure assessment;*



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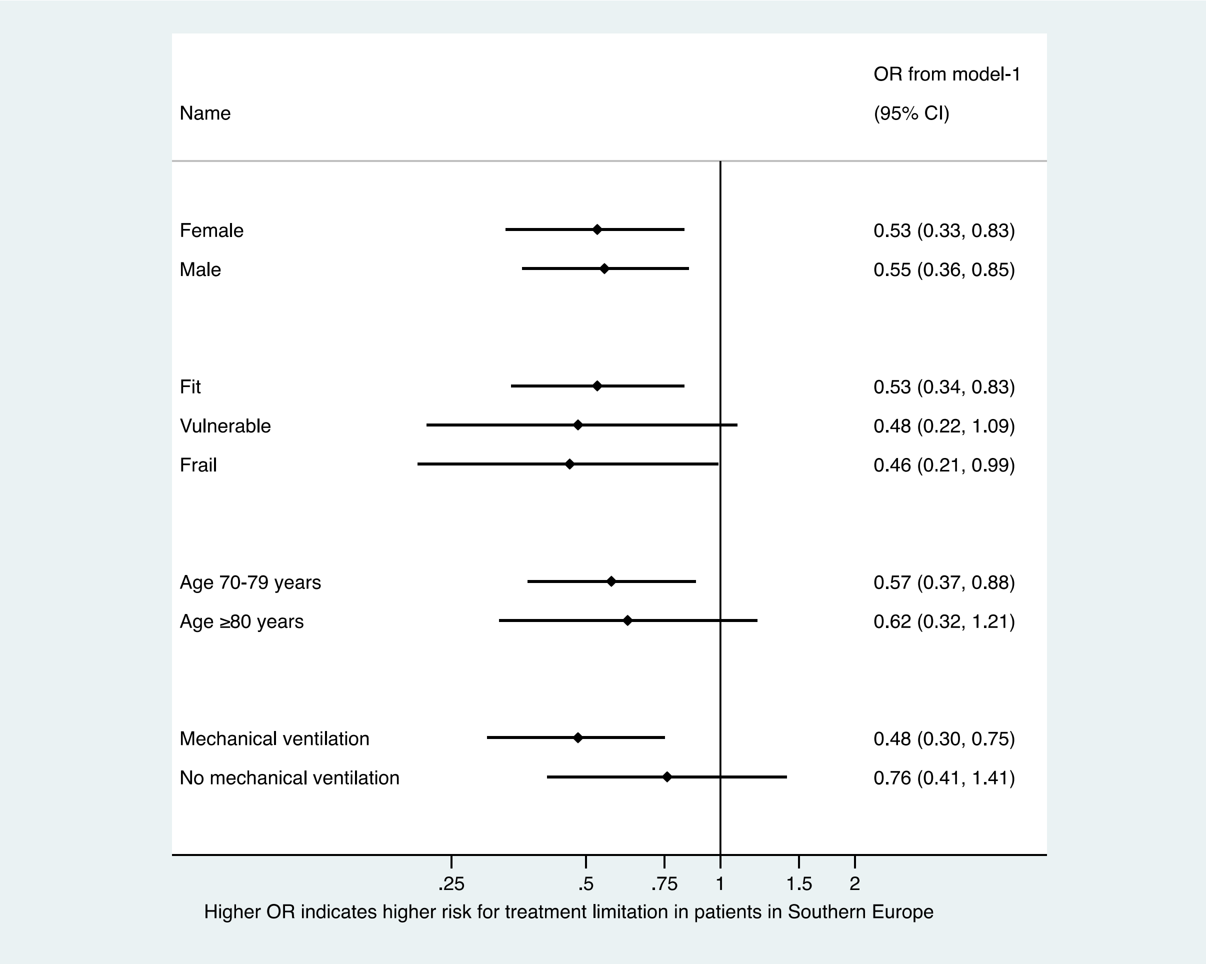
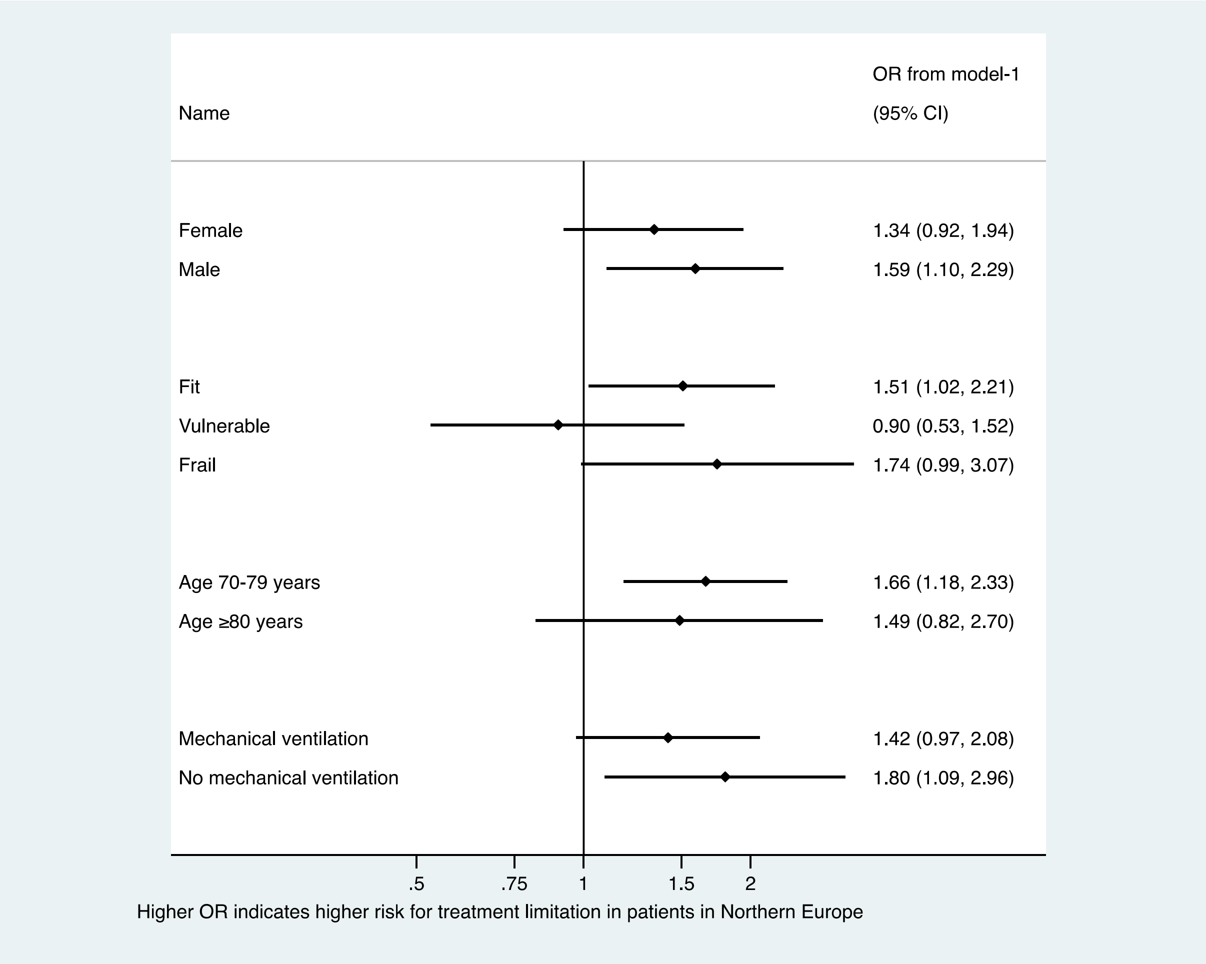


Figure 2: Sensitivity analyses stratifying any treatment limitations in subgroups for patient-specific characteristics using generalised estimation equations (GEE) producing population average odds ratios. The depicted aORs from model-1 include only the ICU as panel. *Abbreviations: aOR: adjusted odds ratio; ICU: intensive care unit;*



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