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LATE BREAKER ARTICLE

OPEN

Influence of Age in End-of-Life Practices in Worldwide ICUs (ETHICUS-2): A Prospective Observational Study

OBJECTIVES: The practice of limiting life-sustaining therapy (LST) at end-of-life is widespread globally. The goal of this study was to evaluate whether patient's age influences end-of-life limitations overall and of various LST in ICUs worldwide.

DESIGN: Multinational, multicenter, prospective observational study.

SETTING: One hundred ninety-nine ICUs in 36 countries worldwide.

PATIENTS: Consecutive adult patients admitted to ICUs who died and/or had LST limitations (withholding, withdrawing, or active shortening of the dying process) were included during a 6-month period between September 2015 and September 2016.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Patients were grouped: younger than 65 years, 65–79 years old, and 80 years old or older. A total of 12,200 patients were included. In multivariate logistic regression analysis, odds ratio (OR) for any LST limitation in the 80 years old or older group was higher than in younger than the 65 years old group (OR 1.47 [95% CI, 1.22–1.76], $p < 0.001$). When stratified by region, this association was significant in Central and Southern Europe (OR 1.56 [95% CI, 1.11–2.20], $p = 0.037$ and OR 2.23 [95% CI, 1.58–3.17], $p < 0.001$, respectively), but not in the other regions. The proportion of withholding therapy of each LST was highest in the group of individuals 80 years or older, whereas the proportion of withdrawing therapy was highest in the group younger than 65 years. The 80-year-old or older group also had a shorter time from ICU admission to first limitation. The predominant reason for any LST limitation in all age groups was unresponsiveness to maximal therapy, followed by neurologic and chronic diseases. Patient age was rarely the primary reason for limitations for all groups.

CONCLUSIONS: End-of-life limitations were higher in patients 80 years or older compared to those 65 years old or younger, with regional variations. The main reasons for limitations were comparable across age groups, with age not being the primary reason.

KEYWORDS: age; end-of-life; intensive care unit; life-sustaining therapy limitation

Limitations of life-sustaining therapy (LST) at end-of-life has become common practice around the world (1–6). Previous studies reported that 8.6–13.2% of patients admitted to ICUs have LST limitations at the end-of-life (2, 3, 5). LST limitations prevent non-beneficial treatments and unnecessary distress in patients and families.

Previous studies reported that age, sex, religion, country, region, advance directives, pre-ICU quality of life, acute and chronic diseases, ICU severity scores, family wishes, and ICU length of stay are associated with the decision to

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KEY POINTS

Question: Does age influence life-sustaining therapy (LST) limitations at end-of-life in ICUs worldwide?

Findings: In this multinational, multicenter, prospective observational study of 12,200 adult patients admitted to ICUs who died and/or had LST limitations, the end-of-life limitations were higher in patients 80 years old or older compared to those younger than 65 years. When stratified by region, this association was significant in Central and Southern Europe, but not in the other regions. The proportion of withholding therapy of each LST was highest in the group 80 years or older, whereas the proportion of withdrawing therapy was highest in the group younger than 65 years. The group 80 years or older also had a shorter time from ICU admission to first limitation. Patient age was rarely the primary reason for limitations.

Meaning: End-of-life LST limitations were more common in patients aged 80 or older than in those under 65 years, varied by region, and were rarely based primarily on age.

limit LST at end-of-life (2, 4, 7–12). Although age is a critical factor for LST limitations at end-of-life (8–15), the association between age and LST limitations has not been explicitly studied globally. Only one study tangentially investigated this relationship globally (5). Furthermore, it is unknown how age contributes as a reason for LST limitations (10, 15, 16).

This study aimed to examine the association between patient age and overall as well as various limitations of end-of-life LST in ICUs globally.

MATERIALS AND METHODS

Study Design, Setting, and Participants

This was a planned sub-study of Ethics in the ICU (ETHICUS-2), a multinational, multicenter, prospective observational study with inclusion criteria of consecutive ICU patients (older than 13 yr) who died and/or had LST limitations over a 6-month period, selected by each participating ICU between September 2015 and September 2016 (17). Exclusion criteria were patients discharged alive with no limitations.

Patients were followed until ICU discharge, death, or 2 months from the first decision to limit life-prolonging therapies. Countries participating were grouped into the following regions: Africa, Latin America, North America, Asia, Australia/New Zealand, Central Europe, Northern Europe, and Southern Europe.

A waiver of informed consent and institutional review board approval, in compliance with the Declaration of Helsinki, was obtained for each participating center (17). The full institutional review board list can be found in the Supplemental appendix (<https://links.lww.com/CCM/H920>).

Data Collected

ETHICUS-2 data were completed by each institution's senior intensivist responsible for end-of-life practices. Patient information collected included age, gender, advanced directives, legal representative, religious affiliation, ICU admission diagnosis, chronic disorders, end-of-life category, dates and times of hospital and ICU admission and discharge, death or discharge from the ICU or hospital, situation at LST limitation decisions, time from ICU admission to first LST limitation, types of LST including mechanical ventilation and dialysis-hemofiltration, ICU and hospital survival or mortality, and reasons for LST limitations. Procedures to improve consistency and reliability included using standardized definitions for end-of-life therapies, unified data collection forms completed by each institution's senior intensivist responsible for end-of-life practices, and a quality assurance program (17).

Outcome

End-of-life therapies were classified into five mutually exclusive categories: withholding or withdrawing LST, active shortening of the dying process, failed cardiopulmonary resuscitation (CPR), and brain death. Patients with brain death were excluded from this sub-study. The primary outcome was whether patients in each age group underwent any LST limitation (withholding or withdrawing LST, or active shortening of the dying process). Secondary outcomes were the differences in LST limitations and reasons for LST limitations.

Statistical Analysis

Patients were grouped into younger than 65 years, 65–79 years, and 80 years old or older (18). Non-normally

distributed continuous data were presented as medians and interquartile ranges and were compared using the Wilcoxon rank-sum test. Categorical data were summarized as percentages and counts, and compared

using Fisher exact test or χ^2 test. For the primary outcome, a multivariate logistic regression analysis was conducted to adjust for differences in patients' characteristics and their condition related to therapy

TABLE 1.
Characteristics and Prognosis of the Study Patients

		Younger Than 65 Yr Old, <i>n</i> = 4602	65–79 Yr Old, <i>n</i> = 4744	80 Yr Old or Older, <i>n</i> = 2854	<i>p</i>
Gender					
Male	<i>n</i> (%)	2901 (63.0)	2905 (61.2)	1485 (52.0)	< 0.001
Advanced directive					
Yes	<i>n</i> (%)	429 (9.3)	440 (9.3)	318 (11.1)	< 0.001
No	<i>n</i> (%)	3579 (77.8)	3817 (80.5)	2305 (80.8)	
Not applicable ^{a)}	<i>n</i> (%)	594 (12.9)	487 (10.3)	231 (8.1)	
Legal representative					
Yes	<i>n</i> (%)	1370 (29.8)	1187 (25.0)	753 (26.4)	< 0.001
No	<i>n</i> (%)	2574 (55.9)	3057 (64.4)	1861 (65.2)	
Not applicable ^{a)}	<i>n</i> (%)	658 (14.3)	500 (10.5)	240 (8.4)	
Region					
Europe					
North	<i>n</i> (%)	777 (16.9)	947 (20.0)	459 (16.1)	< 0.001
Central	<i>n</i> (%)	1140 (24.8)	1500 (31.6)	1092 (38.3)	
South	<i>n</i> (%)	825 (17.9)	997 (21.0)	539 (18.9)	
America					
North	<i>n</i> (%)	457 (9.9)	322 (6.8)	131 (4.6)	
Latin	<i>n</i> (%)	227 (4.9)	176 (3.7)	137 (4.8)	
Africa	<i>n</i> (%)	127 (2.8)	28 (0.6)	5 (0.2)	
Australia/New Zealand	<i>n</i> (%)	170 (3.7)	206 (4.3)	137 (4.8)	
Asia	<i>n</i> (%)	879 (19.1)	568 (12.0)	354 (12.4)	
Patients' religion					
Catholic	<i>n</i> (%)	916 (19.9)	1163 (24.5)	823 (28.8)	< 0.001
Protestant	<i>n</i> (%)	270 (5.9)	382 (8.1)	266 (9.3)	
Islam	<i>n</i> (%)	304 (6.6)	147 (3.1)	67 (2.4)	
Jewish	<i>n</i> (%)	85 (1.9)	117 (2.5)	69 (2.4)	
Buddhist	<i>n</i> (%)	69 (1.5)	53 (1.1)	45 (1.6)	
Hindu	<i>n</i> (%)	87 (1.9)	40 (0.8)	2 (0.1)	
Greek Orthodox	<i>n</i> (%)	106 (2.3)	177 (3.7)	83 (2.9)	
Christian	<i>n</i> (%)	307 (6.7)	258 (5.4)	104 (3.6)	
None	<i>n</i> (%)	810 (17.6)	583 (12.3)	307 (10.8)	
Other	<i>n</i> (%)	64 (1.4)	47 (1.0)	19 (0.7)	
Unknown	<i>n</i> (%)	1584 (34.4)	1777 (37.5)	1069 (37.5)	

(Continued)

TABLE 1. (Continued)
Characteristics and Prognosis of the Study Patients

		Younger Than 65 Yr Old, <i>n</i> = 4602	65–79 Yr Old, <i>n</i> = 4744	80 Yr Old or Older, <i>n</i> = 2854	<i>p</i>
Physicians' religion ^b					
Catholic	<i>n</i> (%)	952/3796 (25.1)	1165/4086 (28.5)	736/2518 (29.2)	< 0.001
Protestant	<i>n</i> (%)	271/3796 (7.1)	346/4086 (8.5)	244/2518 (9.7)	
Islam	<i>n</i> (%)	151/3796 (4.0)	135/4086 (3.3)	82/2518 (3.3)	
Jewish	<i>n</i> (%)	126/3796 (3.3)	107/4086 (2.6)	60/2518 (2.4)	
Buddhist	<i>n</i> (%)	41/3796 (1.0)	40/4086 (1.0)	33/2518 (1.3)	
Hindu	<i>n</i> (%)	112/3796 (3.0)	78/4086 (1.9)	37/2518 (1.5)	
Greek Orthodox	<i>n</i> (%)	108/3796 (2.8)	184/4086 (4.5)	83/2518 (3.3)	
Christian	<i>n</i> (%)	244/3796 (6.4)	280/4086 (6.9)	150/2518 (6.0)	
None	<i>n</i> (%)	1206/3796 (31.8)	1117/4086 (27.3)	673/2518 (26.7)	
Other	<i>n</i> (%)	28/3796 (0.7)	26/4086 (0.6)	13/2518 (0.5)	
Unknown	<i>n</i> (%)	557/3796 (14.7)	608/4086 (14.9)	407/2518 (16.2)	
Acute diagnosis at admission ^c					
Neurologic diseases	<i>n</i> (%)	976 (21.2)	908 (19.1)	497 (17.4)	< 0.001
Surgery	<i>n</i> (%)	960 (20.9)	1139 (24.0)	713 (25.0)	< 0.001
Respiratory diseases	<i>n</i> (%)	2033 (44.2)	2090 (44.1)	1174 (41.1)	0.019
Cardiovascular diseases	<i>n</i> (%)	1074 (23.3)	1334 (28.1)	949 (33.3)	< 0.001
Gastrointestinal diseases	<i>n</i> (%)	790 (17.2)	549 (11.6)	260 (9.1)	< 0.001
Metabolic diseases	<i>n</i> (%)	1109 (24.1)	1032 (28.1)	585 (20.5)	< 0.001
Hematologic diseases	<i>n</i> (%)	335 (7.3)	199 (4.2)	36 (1.3)	< 0.001
Trauma	<i>n</i> (%)	137 (3.0)	106 (2.2)	83 (2.9)	0.056
Sepsis	<i>n</i> (%)	1324 (28.8)	1284 (27.1)	650 (22.8)	< 0.001
Miscellaneous	<i>n</i> (%)	287 (6.2)	219 (4.6)	137 (4.8)	< 0.001
Chronic disorder ^c					
None	<i>n</i> (%)	665 (14.5)	262 (5.5)	112 (3.9)	< 0.001
Cardiovascular diseases	<i>n</i> (%)	1511 (32.8)	3023 (63.7)	2201 (77.1)	< 0.001
Neurologic-Cognitive diseases	<i>n</i> (%)	646 (14.0)	790 (16.7)	666 (23.3)	< 0.001
Chest diseases	<i>n</i> (%)	875 (19.0)	1369 (28.9)	660 (23.1)	< 0.001
Kidney and urinary system diseases	<i>n</i> (%)	461 (10.0)	715 (15.1)	533 (18.7)	< 0.001
Digestive diseases	<i>n</i> (%)	716 (15.6)	444 (9.4)	168 (5.9)	< 0.001
Immunologic diseases	<i>n</i> (%)	537 (11.7)	306 (6.5)	82 (2.9)	< 0.001
General history	<i>n</i> (%)	1551 (33.7)	1817 (38.3)	935 (32.8)	< 0.001
Cancer	<i>n</i> (%)	893 (19.4)	779 (16.4)	242 (8.5)	< 0.001
Unknown	<i>n</i> (%)	126 (2.7)	82 (1.7)	47 (1.7)	0.001

(Continued)

TABLE 1. (Continued)
Characteristics and Prognosis of the Study Patients

		Younger Than 65 Yr Old, <i>n</i> = 4602	65–79 Yr Old, <i>n</i> = 4744	80 Yr Old or Older, <i>n</i> = 2854	<i>p</i>
Mentally competent status at the time a decision was made for limitation					
Yes	<i>n</i> (%)	611 (13.3)	832 (17.5)	592 (20.7)	< 0.001
No	<i>n</i> (%)	3669 (79.7)	3706 (78.1)	2138 (74.9)	
Not applicable ^{a)}	<i>n</i> (%)	322 (7.0)	206 (4.3)	124 (4.4)	
Was information about patient's treatment desires regarding cardiopulmonary resuscitation, withholding or withdrawing therapy, or shortening the dying process at any time asked or received?					
Yes	<i>n</i> (%)	2221 (48.3)	2492 (52.5)	1546 (54.2)	< 0.001
No	<i>n</i> (%)	1969 (42.8)	1937 (40.8)	1155 (40.5)	
Not applicable ^{a)}	<i>n</i> (%)	412 (9.0)	315 (6.6)	153 (5.4)	
Was withholding, withdrawing, or shortening the dying process discussed with patient? ^d					
Yes	<i>n</i> (%)	431/3814 (11.3)	627/4102 (15.3)	451/2524 (17.9)	< 0.001
No	<i>n</i> (%)	3383/3814 (88.7)	3475/4102 (84.7)	2073/2524 (82.1)	
Was withholding, withdrawing, or shortening the dying process discussed with family? ^e					
Yes	<i>n</i> (%)	3159/3814 (82.8)	3300/4100 (80.5)	2015/2524 (79.9)	0.003
No	<i>n</i> (%)	655/3814 (17.2)	800/4100 (19.5)	509/2524 (20.2)	
Length of ICU stay	Days, median (IQR)	5.0 (2.0–12.0)	5.0 (2.0–12.0)	4.0 (2.0–9.0)	< 0.001
Length of hospital stay	Days, median (IQR)	10.0 (4.0–24.0)	11.0 (4.0–24.0)	9.5 (4.0–21.0)	< 0.001
ICU mortality	<i>n</i> (%)	3647 (79.3)	3630 (76.5)	1938 (67.9)	< 0.001
Hospital mortality	<i>n</i> (%)	3895 (84.6)	3962 (83.5)	2213 (77.5)	< 0.001

IQR = interquartile range.

^{a)}“Not applicable” was selected when it cannot be performed by national guidelines or law, etc.

^{b)}Missing data: younger than 65 yr old; *n* = 806, 65–79 yr old; *n* = 658, 80 yr old or older; *n* = 336.

^{c)}*n* (%) in these columns do not add up to the total (100%), as each patient may have had > 1 acute diagnosis at admission, or > 1 chronic disorder.

^{d)}Missing data: younger than 65 yr old; *n* = 788, 65–79 yr old; *n* = 642, 80 yr old or older; *n* = 330.

^{e)}Missing data: younger than 65 yr old; *n* = 788, 65–79 yr old; *n* = 644, 80 yr old or older; *n* = 330.

limitation. The variables applied to the multivariate logistic regression analysis were age, sex, advanced directives, legal representative, region, patients' religion, acute diagnosis at admission, chronic disorder, mental competency at the time of limitation decisions, and information about patients' treatment desires. The variables applied to the multivariate logistic regression analysis were selected based on previous studies (2, 5, 7, 8, 12, 16). The multivariate logistic regression analysis was also performed stratified by region. For Africa, the multivariate logistic regression analysis was performed

without advanced directives and legal representatives because there were none. Data were presented as odds ratio (OR) with 95% CI. *p* values were two-sided and *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of the initially included 12,850 patients, 650 (5.1%) brain death patients were excluded. The remaining

12,200 patients were grouped by age: 4,602 (37.7%) younger than 65 years, 4,744 (38.9%) 65–79 years, and 2,854 (23.4%) 80 years old or older.

Patient characteristics are presented in **Table 1**. The 80 years old or older group had the highest proportion of advanced directives (11.1%, $p < 0.001$). The younger than 65 years group had the highest proportion of legal representatives (29.8%, $p < 0.001$). The numbers of patients in each age group were highest in Central Europe, followed by Southern Europe and Northern Europe. The main patients' religion in each age group was Catholic, followed by no religion. The most common acute diagnosis at admission among each age group was respiratory diseases, followed by cardiovascular diseases and sepsis. Regarding chronic disorders, cardiovascular diseases (77.1%), neurologic-cognitive diseases (23.3%), and kidney and urinary system diseases (18.7%) were highest in the 80 years old or older group. Digestive diseases (15.6%), immunologic diseases (11.7%), and cancer (19.4%) were most prevalent in the group younger than 65 years. The most mentally competent patients at the time of limitation decisions

were the 80 years old or older group (20.7%, 17.5% in the 65–79 yr old group and 13.3% in the younger than 65 yr old group; $p < 0.001$). Information about patients' treatment desires (54.2%), and limitation discussions with the patient (17.9%) were greatest in the 80 years old or older group (patients' treatment desires information: 52.2% in the 65–79 yr old group, 48.3% in the younger than 65 yr old group; $p < 0.001$; patients' limitation discussions: 15.3% in the 65–79 yr group, 11.3% in the younger than 65 yr old group; $p < 0.001$). Approximately 80% of patients across all age groups discussed limitations with their families with the highest proportion in the younger than 65 years old group ($p = 0.003$). Length of ICU and hospital stay were shortest in the 80 years old or older group (median 4.0 and 9.5 d, $p < 0.001$, respectively), and ICU and hospital mortality were highest in the younger than 65 years old group (79.3 and 84.6%, $p < 0.001$, respectively).

Table 2 summarizes end-of-life practices and the prognoses. The highest proportion of any LST limitation was the 80 years old or older group (88.2%), followed by

TABLE 2.
Characteristics of and Prognosis by End-of-Life Practice

		Younger Than 65 Yr, <i>n</i> = 4602	65–79 Yr Old, <i>n</i> = 4744	80 Yr Old or Older, <i>n</i> = 2854	<i>p</i>
End-of-life pathway					
Any limitation	<i>n</i> (%)	3796 (82.5)	4087 (86.2)	2518 (88.2)	< 0.001
Withhold	<i>n</i> (%)	1880 (40.9)	2181 (46.0)	1600 (56.1)	
Withdraw	<i>n</i> (%)	1891 (41.1)	1883 (39.7)	906 (31.7)	
Shortening of the dying process	<i>n</i> (%)	25 (0.5)	23 (0.5)	12 (0.4)	
No limitation (cardiopulmonary resuscitation performed)	<i>n</i> (%)	806 (17.5)	657 (13.9)	336 (11.8)	
Time from ICU admission to first limitation of therapy ^a	Median hours (interquartile range)	59.7 (15.3–190.8)	42.8 (7.3–164.2)	18.7 (1.5–90.6)	< 0.001
ICU mortality					
Any limitations	<i>n</i> (%)	2841/3796 (74.8)	2973/4087 (72.7)	1602/2518 (63.6)	< 0.001
No limitation	<i>n</i> (%)	806/806 (100.00)	657/657 (100.00)	336/336 (100.00)	
Hospital mortality					
Any limitations	<i>n</i> (%)	3089/3796 (81.4)	3305/4087 (80.9)	1877/2518 (74.5)	< 0.001
No limitation	<i>n</i> (%)	806/806 (100.00)	657/657 (100.00)	336/336 (100.00)	

^aStudy population: younger than 65 yr old; $n = 3796$, 65–79 yr old; $n = 4085$, 80 yr old or older; $n = 2518$.

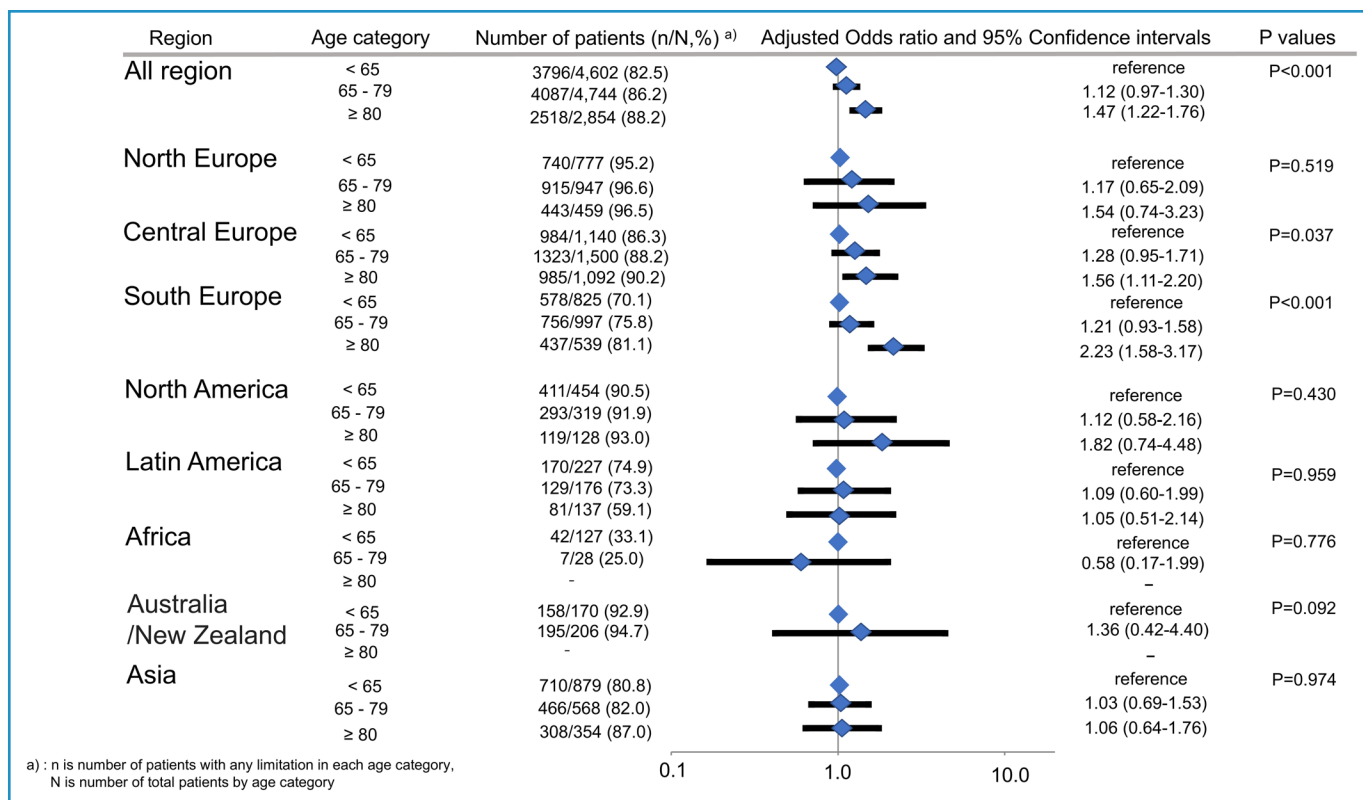


Figure 1. Multivariate logistic regression analysis for any limitation of therapy at the end-of-life in all regions and each region.

the 65–79 years group (86.2%), and the younger than 65 years old group (82.5%) ($p < 0.001$). Although withholding therapy was highest in the 80 years old or older group (56.1%), then the 65–79 years old group (46.0%), and the younger than 65 years old group (40.9%) ($p < 0.001$), withdrawing therapy was highest in the younger than 65 years old group (41.1%), followed by the 65–79 years old group (39.7%), and the 80 years old or older group (31.7%) ($p < 0.001$). The median time from ICU admission to first LST limitation was shortest in the 80 years old or older group (18.7 hr), followed by the 65–79 years group (42.8 hr), and the younger than 65 years old group (59.7 hr) ($p < 0.001$). ICU and hospital mortality among patients with any LST limitation were the highest in the younger than 65 years old group (74.8 and 81.4%, $p < 0.001$, respectively).

Figure 1 shows the primary outcome of the multivariate logistic regression analysis for any LST limitation. The OR for any LST limitation between the younger than 65 years old group and the 65 to 79 y group was not significant (OR 1.12 [95% CI, 0.97–1.30], $p = 0.119$). The OR for any LST limitation in the 80 years old or older group, however, was significantly higher compared with the younger than 65 years old group (OR 1.47 [95% CI, 1.22–1.76], $p < 0.001$). When

stratified by region, the OR for any LST limitation in the 80 years old or older group was significantly higher compared with the younger than 65 years old group in Central Europe and Southern Europe ($p = 0.037$ and $p < 0.001$) but not for the other regions.

Table 3 shows limitation and continuation of each LST. The proportion of withholding therapy of CPR, endotracheal tube, mechanical ventilation, vasopressors, total parenteral nutrition, enteral feedings, dialysis–hemofiltration, and sedation or analgesia was highest in the 80 years old or older group, followed by the 65–79 years old group, and the younger than 65 years old group. The proportion of withdrawing therapy was highest in the younger than 65 years old group, followed by the 65–79 years old group, and the 80 years old or older group. On the other hand, the proportion of continuation of endotracheal tube, mechanical ventilation, vasopressors, and dialysis–hemofiltration was highest in the younger than 65 years old group, followed by the 65–79 years old group, and the 80 years old or older group (each category, $p < 0.001$).

Table 4 shows the reasons for LST limitations. The most common reason for LST limitations in each age group was unresponsiveness to maximal therapy,

TABLE 3.
Limitation and Continuation of Each Life-Sustaining Therapy

Life-Sustaining Therapy		Younger Than 65 Yr Old, n = 3796	65–79 Yr Old, n = 4087	80 Yr Old or Older, n = 2518	p
No cardiopulmonary resuscitation					
Withhold	n (%)	3101 (81.7)	3512 (85.9)	2242 (89.0)	< 0.001
Withdraw	n (%)	285 (7.5)	242 (5.9)	114 (4.5)	
Continued	n (%)	85 (2.2)	117 (2.9)	55 (2.2)	
Not applicable ^a	n (%)	325 (8.6)	216 (5.3)	107 (4.3)	
Endotracheal tube					
Withhold	n (%)	641 (16.9)	998 (24.4)	900 (35.7)	< 0.001
Withdraw	n (%)	520 (13.7)	377 (9.2)	171 (6.8)	
Continued	n (%)	2347 (61.8)	2385 (58.4)	1211 (48.1)	
Not applicable ^a	n (%)	288 (7.6)	327 (8.0)	236 (9.4)	
Mechanical ventilation					
Withhold	n (%)	617 (16.3)	874 (21.4)	789 (31.3)	< 0.001
Withdraw	n (%)	682 (18.0)	534 (13.1)	242 (9.6)	
Continued	n (%)	2220 (58.5)	2365 (57.9)	1256 (49.9)	
Not applicable ^a	n (%)	277 (7.3)	314 (7.7)	231 (9.2)	
Vasopressors					
Withhold	n (%)	749 (19.7)	993 (22.8)	645 (25.6)	< 0.001
Withdraw	n (%)	741 (19.5)	663 (16.2)	301 (12.0)	
Continued	n (%)	1619 (42.7)	1706 (41.8)	1022 (40.6)	
Not applicable ^a	n (%)	687 (18.1)	785 (19.2)	550 (21.8)	
Total parenteral nutrition					
Withhold	n (%)	190 (5.0)	263 (6.4)	187 (7.4)	< 0.001
Withdraw	n (%)	242 (6.4)	173 (4.2)	74 (3.0)	
Continued	n (%)	603 (15.9)	649 (15.9)	378 (15.0)	
Not applicable ^a	n (%)	2761 (72.7)	3002 (73.5)	1879 (74.6)	
Enteral feedings					
Withhold	n (%)	194 (5.1)	245 (6.0)	176 (7.0)	< 0.001
Withdraw	n (%)	482 (12.7)	347 (8.5)	135 (5.4)	
Continued	n (%)	1544 (40.7)	1816 (44.4)	1039 (41.2)	
Not applicable ^a	n (%)	1576 (41.5)	1679 (41.1)	1168 (46.4)	
IV fluids					
Withhold	n (%)	141 (3.7)	161 (3.9)	79 (3.1)	< 0.001
Withdraw	n (%)	483 (12.7)	362 (8.9)	160 (6.4)	
Continued	n (%)	2802 (73.8)	3195 (78.2)	2072 (82.3)	
Not applicable ^a	n (%)	370 (9.8)	369 (9.0)	207 (8.2)	

(Continued)

TABLE 3. (Continued)
Limitation and Continuation of Each Life-Sustaining Therapy

Life-Sustaining Therapy		Younger Than 65 Yr Old, <i>n</i> = 3796	65–79 Yr Old, <i>n</i> = 4087	80 Yr Old or Older, <i>n</i> = 2518	<i>p</i>
Dialysis–hemofiltration ^b					
Withhold	<i>n</i> (%)	963 (25.4)	1210 (29.6)	950 (37.7)	< 0.001
Withdraw	<i>n</i> (%)	352 (9.3)	294 (7.2)	121 (4.8)	
Continued	<i>n</i> (%)	653 (17.2)	651 (15.9)	253 (10.1)	
Not applicable ^a	<i>n</i> (%)	1828 (48.1)	1931 (47.3)	1194 (47.4)	
Sedation or analgesia ^c					
Withhold	<i>n</i> (%)	69 (1.8)	87 (2.1)	62 (2.5)	< 0.001
Withdraw	<i>n</i> (%)	201 (5.3)	116 (2.9)	46 (1.8)	
Continued	<i>n</i> (%)	2884 (76.0)	3199 (78.3)	1926 (76.5)	
Not applicable ^a	<i>n</i> (%)	641 (16.9)	683 (16.7)	484 (19.2)	

^a“Not applicable” was selected when it cannot be performed by national guidelines or law, etc.

^bMissing data: 65–79 yr old; *n* = 1.

^cMissing data: younger than 65 yr old; *n* = 1, 65–79 yr old; *n* = 2.

followed by neurologic and chronic disease. Patient requests as the primary reason for limitations were the highest in the 80 years old or older group (13.0%), followed by the 65–79 years old group (9.2%), and the younger than 65 years old group (4.9%). Patient age as the primary reason for limitations was null or very low within all age groups (0.0–3.9%). The most important primary consideration for physicians’ decision-making for each age group was best interest of the patient (45.1–45.7%), followed by good medical practice (36.0–39.4%). The highest proportion of patient autonomous decisions was observed in the 80 years old or older group (12.9%), followed by the 65–79 years old group (10.5%), and the younger than 65 years old group (6.8%). Patients with living wills as the important primary consideration for physicians’ decision making was low (1.1–2.2%). Most physicians did not face difficulties in making end-of-life decisions (85.8–90.2%). Disagreements (3.3–5.1%) and legal issues (3.0–3.7%) were a distant second and third, as the next most common difficulties.

DISCUSSION

This is the first study demonstrating the influence of age on overall limitations of LST and specific LST for end-of-life practices in ICUs worldwide. The study demonstrated that patients 80 years old or older had more LST limitations than patients younger than 65

years old. LST limitations increased with the patients’ age. However, regional differences existed. When stratified by region, patients 80 years old or older had more LST limitations than patients younger than 65 years in Central and Southern Europe, in contrast to Northern Europe, North America, South America, and Asia. The proportion of withholding therapy of each LST was highest in the 80 years old or older group, whereas the proportion of withdrawing therapy was highest in the younger than 65 years old group. The 80 years old or older group also had a shorter time from ICU admission to first limitation. The primary reasons for LST limitations and the important primary considerations for physicians’ decision-making of limitations were similar for each age category, that is, unresponsiveness to maximal therapy, followed by neurologic disorders, and best interest of the patient, thereafter by good medical practice, respectively. Patient age was rarely the primary reason for limitations.

In studies performed in individual countries before the COVID-19 pandemic, older age was inconsistently reported as a factor independently associated with LST limitations (8–15, 19). Also, in studies performed in individual countries and European countries during the COVID-19 pandemic, older age was not consistently identified as an independent factor associated with LST limitations (20–22). In the only one previous worldwide study, age was not associated with limitations of

TABLE 4.
Reasons, Consideration, and Difficulties for the Limitation of Therapy at the End-of-Life

		Younger Than 65 Yr Old, <i>n</i> = 3796	65–79 Yr Old, <i>n</i> = 4087	80 Yr Old or Older, <i>n</i> = 2518	<i>p</i>
Primary reason for withholding, withdrawing, or shortening the dying process ^a					
Sepsis/septic shock	<i>n</i> (%)	69/3748 (1.8)	80/4049 (2.0)	48/2501 (1.9)	< 0.001
Multiple-system organ failure	<i>n</i> (%)	368/3748 (9.8)	427/4049 (10.5)	230/2501 (9.2)	
Neurologic	<i>n</i> (%)	718/3748 (19.2)	698/4049 (17.2)	350/2501 (14.0)	
Chronic disease	<i>n</i> (%)	412/3748 (11.0)	589/4049 (14.5)	337/2501 (13.5)	
Patient request	<i>n</i> (%)	185/3748 (4.9)	374/4049 (9.2)	326/2501 (13.0)	
Family request	<i>n</i> (%)	280/3748 (7.5)	205/4049 (5.1)	153/2501 (6.1)	
Poor quality of life	<i>n</i> (%)	175/3748 (4.9)	209/4049 (5.2)	186/2501 (7.4)	
Unresponsiveness to maximal therapy	<i>n</i> (%)	1409/3748 (37.6)	1354/4049 (33.4)	708/2501 (28.3)	
Age	<i>n</i> (%)	0/3748 (0.0)	6/4049 (0.1)	98/2501 (3.9)	
Other	<i>n</i> (%)	132/3748 (3.5)	107/4049 (2.6)	65/2501 (2.6)	
Primary important consideration for physicians' decision-making ^a					
Autonomous decision of the patient	<i>n</i> (%)	255/3748 (6.8)	424/4049 (10.5)	322/2501 (12.9)	< 0.001
Best interest of the patient	<i>n</i> (%)	1711/3748 (45.7)	1825/4049 (45.1)	1138/2501 (45.5)	
Cost effectiveness	<i>n</i> (%)	182/3748 (4.9)	70/4049 (1.7)	29/2501 (1.2)	
Good medical practice	<i>n</i> (%)	1474/3748 (39.3)	1595/4049 (39.4)	899/2501 (36.0)	
Legal concerns	<i>n</i> (%)	1/3748 (0.03)	6/4049 (0.1)	6/2501 (0.2)	
Religious principles	<i>n</i> (%)	17/3748 (0.5)	13/4049 (0.3)	3/2501 (0.1)	
Social and pressures	<i>n</i> (%)	3/3748 (0.1)	3/4049 (0.07)	3/2501 (0.1)	
Need for an ICU bed	<i>n</i> (%)	1/3748 (0.03)	3/4049 (0.07)	3/2501 (0.1)	
Living will	<i>n</i> (%)	43/3748 (1.1)	69/4049 (1.7)	55/2501 (2.2)	
Other	<i>n</i> (%)	61/3748 (1.6)	41/4049 (1.0)	43/2501 (1.7)	
Primary difficulties for physicians in either withholding, withdrawing, or shortening the dying process ^a					
Ethical	<i>n</i> (%)	140/3748 (3.7)	122/4049 (3.0)	66/2501 (2.6)	< 0.001
Legal	<i>n</i> (%)	138/3748 (3.7)	133/4049 (3.3)	83/2501 (3.3)	
Disagreements	<i>n</i> (%)	190/3748 (5.1)	137/4049 (3.4)	82/2501 (3.3)	
Religious	<i>n</i> (%)	28/3748 (0.7)	13/4049 (0.3)	8/2501 (0.3)	
None	<i>n</i> (%)	3217/3748 (85.8)	3628/4049 (89.6)	2255/2501 (90.2)	
Other	<i>n</i> (%)	35/3748 (0.9)	16/4049 (0.4)	7/2501 (0.3)	

^aMissing data: younger than 65 yr old; *n* = 48, 65–79 yr old; *n* = 38, 80 yr old or older; *n* = 17.

therapy (5). The present study demonstrated that the 80 years old or older group had more limitations than the younger than 65 years old group. The differences in study findings may reflect differences between countries and regions. The present worldwide study had a higher proportion of patients from European countries (where there were more limitations in the elderly)

than the previous worldwide study which might explain the differences (67.8% vs. 54.3%). Another difference was the composition of the study patients. Study patients in the previous worldwide study were all adult patients admitted to ICUs. Present study patients were ICU patients dying or with LST limitations. Surviving patients without LST might weaken the relationship

between therapy limitations and age. Among LST limitations, withholding therapy was highest in the 80 years old or older group and withdrawing therapy was highest in the younger than 65 years old group. Similarly, limitations of each LST, especially invasive therapy such as mechanical ventilation and dialysis–hemofiltration, had more withholding and less withdrawing among the older age group. This finding was similar to a study conducted in Germany (23). More patients in the 80 years old or older group might not have received otherwise indicated therapies, because of their physicians' view of their poor prognosis, and, thus, procedures not started might not have to be withdrawn.

This study also demonstrated regional differences between age groups and end-of-life LST limitations. Although previous studies showed regional or country differences for therapy limitations (2, 4, 5), few evaluated regional difference of therapy limitations based on age. A systematic review for global variability in withholding and withdrawing LST reported a significant difference between regions for limiting treatment (4). The reported reasons for regional or country-specific differences in therapy limitations included religion, culture, socioeconomic status, and medicolegal considerations (5, 24, 25). The international Intensive Care Over Nations audit noted that limitations of therapy were less frequent in low/lower-middle gross national income (GNI) countries than in high GNI countries (6% vs. 14%, $p < 0.001$) (5). In East Asia, filial piety (respect, reverence, and loyalty a child has toward their parents), avoidance of conflict, and importance of family-centered decision-making may influence therapy limitations (26–28). In addition, the age structure of a country may affect decisions across age groups leading to regional age limitation differences. Modern attitudes toward older adults indicate that recent rises in the aged population significantly predicted negative elderly attitudes (29).

Regarding the impact of age on reasons of end-of-life therapy limitations, previous studies conducted in individual countries reported inconsistent findings. Although one study suggested that older age was the reason for LST limitations (10), others did not show age as the main reason (15, 16). The present study demonstrated that age alone as the reason for limitations was rare, less than 4%. Perhaps biological age is regarded as more important than chronological age. In

addition, physicians may prioritize patient prognosis based more on neurologic status and chronic comorbidities than chronological age.

This study showed that withholding therapy of each LST was highest in the 80 years old or older group and withdrawing therapy was highest in the younger than 65 years old group. More patients in the 80 years old or older group might not receive otherwise indicated therapies, because of their physicians' view of their poor prognosis, and subsequently, therapies not started might not have to be withdrawn. This study also showed that length of ICU and hospital stay were the shortest in the 80 years old or older group. This finding might be associated with the fact that the time from ICU admission to first therapy limitation was the shortest in the 80 years old or older group and that therapy limitations increased as age increased. The shorter time from ICU admission to first limitation and greater therapy limitations in the 80 years old or older group could be related to the fact that the 80 years old or older group had more cardiovascular diseases and neurologic-cognitive diseases as chronic disorders. Also, they were the most mentally competent at the time of limitation decisions, had better knowledge of their treatment preferences, and discussed limitations more often than other groups. Interestingly, this study showed that ICU and hospital mortality were highest in the younger than 65 years old group. This might be related to the finding that ICU and hospital mortality among patients with therapy limitations were the highest in the younger than 65 years old group. Patients with therapy limitations among the younger than 65 years old group might have had more therapy limitations because of more severe illnesses and thus, worse prognosis. Also, the 80 years old or older group might include patients who had a lower predicted mortality risk than the younger than 65 years old group. The younger than 65 years old group might have been more severely ill due to more documented acute diagnoses of sepsis and hematological diseases at admission and more chronic disorders with immunologic diseases and cancer. Severely ill elderly patients are typically not admitted to the ICU and more commonly die on the ward in contrast to younger patients (30).

Limiting treatments at the end-of-life are integral to aligning patient care with their values and perspectives on quality of life. Although patient-initiated requests accounted for a minority of cases

(4.9–13.0%), our study revealed that the main reasons for limitations were unresponsiveness to maximal therapy, neurologic and chronic disease. This suggests that limitations are often made when patients' treatment goals cannot be achieved, emphasizing the importance of understanding individual patient contexts and values in shaping end-of-life care choices. Also, the important primary consideration for physicians' decision-making was predominantly the best interests of the patients and good medical practice. These two reasons far outnumbered the others, with little differences between age groups. The findings of this study showed that age did not play a major part in physicians' decision making.

This study has several strengths. First, according to a prospective design, established end-of-life definitions and methods were used in all participating centers, providing parity in comparisons between regions. Second, physicians responsible for end-of-life decisions and data collection were the same in each center, ensuring consistency. Third, this study was performed worldwide with many patients enrolled over a 6-month period. Finally, multiple data on end-of-life processes were obtained, including reasons for therapy limitations.

This study also has several limitations. First, the number of patients, ICUs and countries participating was skewed by region (**eTable 1**, <https://links.lww.com/CCM/H920>). Patients were mostly from Europe with smaller percentages from other regions. The study was, however, conducted in countries spanning all continents and the primary outcome was stratified by region. Second, the study data were collected 10 years ago. Despite this, there are no new worldwide data on end-of-life care published in the past decade. Third, results may not be applicable to all intensivists because the participating ICU physicians may have been particularly interested in end-of-life care issues. Fourth, results may not be representative for all ICUs of a country since participation was voluntary. Fifth, age may influence ICU admission decisions, with younger patients potentially receiving priority access. Sixth, patient severity scores at the time of the decision of limitation of therapy were not assessed. Finally, there may be differences in legal systems and national guidelines covering end-of-life decisions between countries, affecting physicians' decisions and end-of-life practice. Despite these

limitations, this is the first report of worldwide differences in LST limitations by age groups and also worldwide limitations and continuations of each LST by age groups.

CONCLUSIONS

This study revealed greater end-of-life therapy limitations in patients 80 years old or older compared with those younger than 65 years old, with regional differences. Withholding therapy of each LST is most common highest in patients 80 years old or older; however, withdrawing in those younger than 65 years old. The time from ICU admission to first limitation is shorter in patients 80 years old or older. Patient requests as the primary reason for limitations are highest in the patients 80 years old or older. The primary reasons for LST limitations were not related to age, that is, unresponsiveness to maximal therapy, neurologic disorders, best interest of the patient, and good medical practice, respectively. Advanced age was not the primary reason for LST limitation in all regions.

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