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Limitations of life-sustaining therapies in South Africa

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ABSTRACT

Purpose: Limitations of life sustaining therapies (LLST) are frequent in intensive care units (ICUs), but no previous studies have examined end-of-life (EOL) care and LLST in South Africa (SA).
Materials and methods: This study evaluated LLST in SA from the data of a prospective, international, multicentre, observational study (Ethicus-2) and compared practices with countries in the rest of the world.
Results: LLST was relatively common in SA, and withholding was more frequent than withdrawing therapy. However, withdrawing and withholding therapy were less common, while failed CPR was more common, than in many other countries. No patients had an advance directive. Primary reasons for LLST in SA were poor quality of life, multisystem organ failure and patients' unresponsiveness to maximal therapy. Primary considerations for EOL decision-making were good medical practice and patients' best-interest, with the need for an ICU bed only rarely considered.
Conclusions: Withholding was more common than withdrawing treatment both in SA and worldwide, although both were significantly less frequent in SA compared with the world average.

1. Introduction

End of life (EOL) decisions are frequent in the intensive care unit (ICU). Therefore, limitations of life-sustaining therapy (LLST) are frequently employed in patients with poor prospects for survival or for returning to a meaningful state of health. LLST includes withholding or withdrawing of LLST and even active shortening of the dying process (SDP) in certain jurisdictions [1,2]. Practices vary internationally based on several factors, including religious beliefs, societal norms, legal constraints, individual opinion, and ethical priorities amongst medical staff [3,4]. International consensus documents and expert group statements from professional bodies have formulated agreed definitions and statements that define good end-of-life practice [5-7]; nevertheless, regional factors likely influence the national and international differences seen in actual bedside practice [2].

It is important that each region examine their own practice to identify areas for improvement. In South Africa (SA) there are several potential factors that may influence end-of-life care. ICU resources and bed availability are limited, especially in publicly funded hospitals. For example, it has been estimated that there are approximately 25 ICU beds per 100,000 population in the United States, compared with 5 ICU beds per 100,000 population in the United Kingdom (UK) and 2 public ICU beds per 100,000 population in SA [8,9]. While the type of intensive care unit will influence the types of cases seen in the unit, there is also very good evidence that resource limitations influence the case mix of patients admitted to an ICU [10-13]. This occurs even if admission choices are being informed, by ideal ethical considerations, where the greatest benefit is sought for the greatest number of people [14]. Furthermore, the relative shortage of ICU beds, probably explains why patients admitted to ICUs in the UK and SA, for example, have been found to have more physiological derangements than those admitted in the USA [15]. At the end-of-life all these imperatives may plausibly encourage physicians to make beds available for new admissions by expediting LLST. We therefore hypothesized that in resource limited South African ICUs the frequency of LLST might be higher than in other areas of the world, as was suggested previously [9].

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Despite guidelines on non-beneficial therapies, the decision to limit treatment is often based on clinical judgement, rather than strict consensus definition, or a considered opinion by a committee [16]. Advance directives may aid decision-making, but appear to be rarely seen in SA, and remain uncommon even in developed countries [4], although their use is increasing in Europe and the United States of America [4,17]. Therefore, these difficult decisions are often made by frontline medical staff, independent of knowledge of patient's actual wishes and often without cultural sensitivity or awareness of current guidelines for shared decision-making [18]. Training in end-of-life decisions is lacking in SA and internationally and is often not part of under- or post-graduate training [19].

There are few previous studies evaluating end-of-life care and LLST in South African ICUs. Those studies that exist have mainly investigated withdrawing of life sustaining therapies [9,20]. Therefore, the aim of this study was to compare comprehensively LLST data from a public SA ICU with that of international ICUs.

2. Methods

We examined the South African data from the Ethicus-2, prospective, multi-centre, worldwide cohort study, which evaluated EOL practices in a SA ICU and compared those practices with ICUs in the rest of the world. The South African ICU included in this study, was an adult multidisciplinary ICU, that admitted adult medical, surgical and gynaecological cases from the hospital, and only selected trauma cases, as the hospital has a dedicated trauma unit; in fact, during the study period, no trauma cases were admitted to the ICU. The Ethicus-2 study was an observational study of consecutive adult patients admitted to 199 ICUs in 36 countries, who died or had a LLST (i.e., withholding or withdrawing therapy or active shortening of the dying process (SDP)) during a chosen 6-month period between 1 September 2015 and 30 September 2016 [17]. Each individual centre obtained institutional review board approval according to local requirements.

The current study was a standalone investigation comparing various demographic and clinical characteristics, the reasons, and important considerations for decision-making in patients with LLST from one multidisciplinary ICU in SA, compared with the aggregate data from ICUs in the rest of the world. The data were collected by the senior ICU physician or their designee for each patient after a decision was made to limit life-sustaining therapy, or the death of the patient. Relevant data were entered into the Ethicus-2 case report form as previously described [17]. Definitions of LLST were the same as used in the Ethicus-2 study [17].

The data collected for the current study included the following: age, sex, primary chronic comorbidity, primary ICU admission diagnosis, type of LLST, occurrence of failed CPR or brain death, and mortality. The time from ICU admission to first decision to institute LLST, as well as the time from LLST to death were also recorded. In addition, clinician knowledge of patient preferences regarding LLST and the sources of this information (e.g. presence of an advance directive, information from patient and/or family), the reasons for not discussing LLST with patients and families, and reasons and important considerations for decision-making were collected, as well as the person who first brought up the topic, and whether there was agreement between medical staff, staff and patients, and staff and family. In addition, it was documented whether there were delays in instituting LLST due to disagreements, and what reasons there were that made it difficult for clinicians to make end-of-life decisions.

This was largely a descriptive study. Dichotomous or categorical variable data are presented as number (%), whereas continuous variable data are reported as mean ± standard deviation or median (interquartile range). Proportions were compared between the SA ICU and ICUs from the rest of the world using the Chi-squared test or the Fisher's exact test. Furthermore, distribution normality of continuous variables was assessed by Kolmogorov Smirnov test and times from ICU admission to first LLST and from first LLST to death were compared between the SA ICU and all the other Ethicus 2 ICUs by Mann Whitney *U* test. Significance was set at $P < 0.05$; all reported *P* values are two-tailed. Analyses were conducted with GraphPad Instat version 3.00 and SPSS version 28.0.

3. Results

A total of 87,951 patients were admitted during a 6-month period (882 [1%] to the South African ICU and 87,069 [99%] to ICUs in the rest of the world). Of these, 12,850 patients died or had a LLST and were studied further. Fig. 1 depicts the data from the South African patients. Overall, 118/882 patients (13.4%) in the South African ICU, and 12,732/87,068 patients (14.6%) in the worldwide ICUs died or had a LLST (Table 1) (not significantly different). Withholding was more common than withdrawing treatment both in SA and worldwide, although both were significantly less frequent in SA compared with the worldwide average (28% versus 44.2% [$p < 0.001$] and 16.9% versus 36.6% [$p < 0.0001$], respectively). Failed CPR as the cause of death was substantially more common in SA than the rest of the world (55.1% versus 13.6%; $p < 0.0001$).

Data on mortality are shown in Table 1. Overall, the mortality of all ICU cases was no different in SA (13.3%) than in the rest of the world (12.2%), while the mortality in cases that had a LLST was significantly higher in SA than in the rest of the world (98.1% versus 79.2% [$p = 0.001$]).

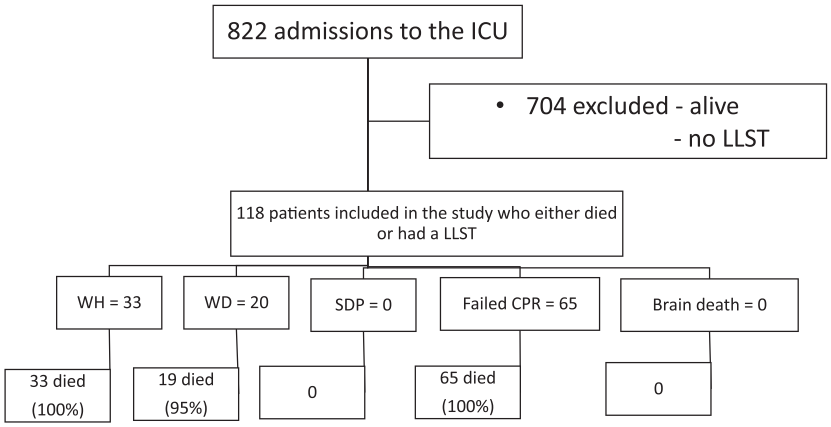
Table 2 shows a comparison of the population characteristics of patients with LLST in SA and the rest of the world. In the South African cohort, patients were younger ($p < 0.001$), with significantly more female patients ($p = 0.002$). Immunological comorbidities were more common ($p < 0.0001$), whereas cardiovascular diseases were less common ($p < 0.0001$). Primary ICU diagnoses were similar, except for metabolic conditions, which were more common in the South African cohort ($p < 0.0001$), and cardiovascular diseases, which were less common ($p = 0.01$) compared to the rest of the world.

Table 3 lists the clinical reasons for implementing LLST in SA patients of which the most common were poor quality of life (88.7%) (locally interpreted as perceived expected poor quality of life should the patients recover from their ICU illness), multisystem organ failure (71.7%) and patient unresponsive to maximal therapy (68.0%), which were also the primary reasons reported. Table 4 lists the most important considerations justifying decision-making in cases with LLST in SA. The key primary considerations were overwhelmingly reported as good medical practice (62.3%), and patient best-interest (35.8%), with the need for an ICU bed being reported as only rarely being a consideration, and never the primary consideration.

The median time from ICU admission to first limitation decision was 4680 min (IQR 1295–8775) in the South African ICU and 2472 min (IQR 401–9422) in the rest of the world ($p = 0.08$). Furthermore, the median time from first limitation to death was 73 min (IQR 41–981) in the South African ICU and 1103 min (IQR 200–4368) in the rest of the world ($p < 0.001$) (Supplementary Table 1).

Table 5 describes clinician knowledge of patient preferences regarding LLST and the sources of this information. No advance directives (AD) were reported in the South African cohort, whereas 10.6% of patients in the rest of the world did have advance directives ($p < 0.001$). There was a significant amount of unavailable data relating to the knowledge of patient preferences as derived from the family in the South African database, and as such, these data have not been included in the table. Table 6 shows the reasons that were given for not discussing LLST with patients and compares SA and the rest of the world. The overwhelming reason was that the patient was unconscious and/or lacked mental capacity (98% versus 93.1% [not significant]). Overall, the available data demonstrated similar practice considerations in SA and the rest of the world.

The person who first brought up the topic of LLST was most often the



CPR = cardiopulmonary resuscitation; ICU = intensive care unit; LLST = limitation of life sustaining treatment; WD = withdrawing; WH = withholding; SDP = shortening of the dying process

Fig. 1. Profile of the ICU patients admitted to the South African ICU.

Table 1
Characteristics of patients who died or had a limitation of life – sustaining therapy (LLST) (n = 12,850).

	South Africa	Rest of the World	P value
Patients, n (percent)	118/882 (13.4%)	12,732/87069 (14.6%)	NS
Withholding	33/118 (28%)	5628/12732 (44.2%)	0.0006
Withdrawing	20/118 (16.9%)	4660/12732 (36.6%)	<0.0001
SDP	0	60 (0.5%)	NS
Failed CPR	65/118 (55.1%)	1734/12732 (13.6%)	<0.0001
Brain death	0	650/12732 (5.1%)	0.0210
Total mortality of ICU cases	117/882 (13.3%)	10,605/87069 (12.2%)	NS
Mortality of cases with LLST	52/53 (98.1%)	8200/10348 (79.2%)	0.0014

ICU = intensive care unit; CPR = cardiopulmonary resuscitation; LLST = limitation of life-sustaining therapy; n = number of patients; NS = not significant; SDP = active shortening of the dying process.

ICU physician (in 52/53 patients, 98.1%). There was generally good agreement between ICU doctors and other treating doctors (in 49/51, 96%), and ICU doctors and nurses (in 50/53, 94%). As expected, agreement between staff and patients occurred seldomly, as most patients were unconscious and/or lacked mental capacity (98%) (Table 6).

In the current study there were delays in instituting LSST due to disagreements amongst stakeholders regarding the decision. There was one patient from South Africa in whom LLST was delayed for this reason, and this was due to the fact that the cardiothoracic surgeon involved did not agree with the decision. In the rest of the world, delays in LLST occurred due to disagreement in 3.6% of cases, with no significant difference compared with SA. However, there were significant differences between SA and the rest of the world regarding reasons that clinicians found it difficult to make end-of-life decisions, with legal (2.8%), ethical (2.6%) and religious issues (0.4%), being more frequent in the rest of the world than in SA (p = 0.015) (Supplementary Table 2).

In those patients where the information on patient and physician religion was known, most patients in the South African cohort who had LLST (38/42 [90.5%]), and many of the doctors involved (24/52 [46.2%]), were Christian or nominally Christian, but there was a broader mix of religions amongst the doctors. There were, however, no significant differences between Christian (22/52 [42.3%]) and non-Christian doctors (28/52 [53.8%]) regarding withholding vs withdrawing therapy (p = 0.40), and no significant difference between the presence of reported religiosity amongst the doctors and withholding (25/32 [78%]) vs. withdrawing therapy (12/20 [60%] (p = 0.21).

Table 2
Population characteristics of patients with LLST (n = 10,401).

	South Africa	Rest of the World	P value
Patient number, %	53/882 (6%)	10,348/87069 (11.9%)	NS
Age, years ± SD	51.7 (18.3)	67.8 (15.2%)	<0.001
Female[†]	33/53 (62.3%)	4157/10348 (40.2%)	
Male[†]	20/53 (37.7%)	6191/10348 (59.8%)	
Chronic comorbidity[‡]			
Immunological	18 (34%)	223 (2.2%)	<0.0001
Cancer	6 (11.3%)	1096 (10.6%)	NS
Cardiovascular disease	4 (7.5%)	4195 (40.5%)	<0.0001
Chest diseases	3 (5.7%)	1102 (10.6%)	NS
General History	2 (3.8%)	995 (9.6%)	NS
Kidney and urinary tract diseases	1 (1.9%)	386 (3.7%)	NS
Neurological, cognitive, muscular disorders	0	814 (7.9%)	0.0614
Gastrointestinal	0	547 (5.3%)	NS
Unknown	10 (18.9%)	171 (1.7%)	<0.0001
None	9 (17%)	819 (7.9%)	0.0294
ICU admission diagnosis[‡]			
Surgery	12 (22.6%)	1640 (15.8%)	NS
Respiratory	11 (20.8%)	2992 (29.9%)	NS
Sepsis	10 (18.9%)	1146 (11.4%)	NS
Metabolic	8 (15.1%)	316 (3.1%)	<0.0001
Gastrointestinal	5 (9.4%)	665 (6.4%)	NS
Neurological	3 (5.7%)	1505 (14.5%)	NS
Miscellaneous	2 (3.8%)	154 (1.5%)	NS
Cardiovascular	1 (1.9%)	1652 (16%)	0.0091
Haematological	1 (1.9%)	106 (1.0%)	NS
Trauma	0	142 (1.4%)	NS

LLST = limitation of life-sustaining therapy including withholding or withdrawing therapy and active shortening of the dying process; SD = standard deviation.

[†] Difference in sex distribution was significant (p = 0017).

[‡] Chronic comorbidity and ICU admission diagnosis were the primary diagnosis.

4. Discussion

This prospective, observational study is the first to examine comprehensively LLST practices in a South African ICU. Compared to international findings, results from a single centre public South African ICU showed that LLST was relatively common, that withholding was

Table 3
Reasons for limitation of life sustaining therapy in patients from South Africa including all reasons reported and primary reasons reported for each patient ($n = 53$).

All reasons reported[†]	
Poor quality of life	47 (88.7%)
Multisystem organ failure	38 (71.7%)
Unresponsive to maximal therapy	36 (68.0%)
Underlying chronic disease	30 (56.6%)
Sepsis/septic shock	22 (41.5%)
Neurological cause	16 (30.2%)
Patient/family request	3 (5.7%)
Primary reasons reported[‡]	
Poor quality of life	16 (30.2%)
Multisystem organ failure	15 (28.3%)
Unresponsive to maximal therapy	13 (24.5%)
Neurological cause	6 (11.3%)
Sepsis/septic shock	2 (3.8%)
Other	1 (1.9%)

[†] Frequently multiple reasons in each patient.
[‡] Single most important reason in each patient.

Table 4
Considerations for decision making in cases with LLST in South Africa including all reasons and primary reasons for each patient (53 patients).

All reasons reported[†]	
Good medical practice	52 (98.1%)
Best interest of the patient	49 (92.5%)
Cost-effectiveness	2 (3.8%)
Need for an ICU bed	2 (3.8%)
Living will	1 (1.9%)
Other	1 (1.9%)
Autonomous decision of the patient	0
Legal concerns	0
Religious principles	0
Social reasons and pressures	0
Primary reasons reported[‡]	
Good medical practice	33 (62.3%)
Best interest of the patient	19 (35.8%)
Other	1 (1.9%)

[†] Frequently multiple reasons in each patient.
[‡] Single most important reason in each patient.

more frequently practiced than withdrawing therapy, and that no cases of active SDP occurred. Interestingly, however, both withdrawing and withholding of therapy were substantially less common in SA than other countries. Failed CPR was more common. Since this study did not compare successful versus failed CPR, but rather the occurrence, or not, of CPR prior to death, it would appear that this high frequency of failed CPR most likely demonstrates the frequent provision of aggressive life-sustaining therapy up to the point of death. No patients had an advance directive. The reasons for LLST in SA were poor quality of life, multisystem organ failure and that the patient was unresponsive to maximal therapy. Interestingly, this is similar to the findings in Israeli ICUs reported previously, despite Israel being a high-income country [21]. The key considerations for EOL decision-making were overwhelmingly reported as good medical practice, and patient best-interest, which were also the primary considerations. While the latter, in some jurisdictions, may be considered to represent a paternalistic view to end-of-life decisions, in many centres that decision is most frequently made together with other stakeholders, including the patient and/or patient surrogate. Importantly, the need for an ICU bed only rarely was considered as being an important, and never being the primary consideration.

In many countries LLST is an ethically accepted practice in modern intensive care. Dying patients are frequently encountered in the ICU and

Table 5
Clinician knowledge of patient preferences regarding llst and sources thereof.[†]

	South Africa	Rest of the World	P value
Number of ICUs (number of patients)	1 (118)	198 (12732)	
Source of information regarding patient preference			
AD	0/118 (0%)	1199/11312 (10.6%) [2.6% - 49.3%][‡]	0.0007
Patient	1/4 (25%)	468/6453 (7.3%) [1.2% - 10.4%]	NS
Family	3/4 (75%)	4518/6451 (70.0%) [59% - 88.6%]	NS
Multiple	0/118 (0%)	1368/6454 (21.2%) [9.5% - 31.4%]	<0.0001
Other	0/118 (0%)	96/6454 (1.5%) [0% - 3.2%]	NS

AD = advance directive; ICU's = intensive care units; LLST = limitation of life sustaining treatment.
[†] The denominator of this table includes all the cases that died or had a LLST (n = 12,850) but excludes patients in which this information was not reported.
[‡] The information in the square brackets in this table are the range of percentages in the different regions of the world outside South Africa for which information was known.

Table 6
Reasons for not discussing LLST with the patients.

	South Africa[†]	Rest of the World	P value
Patient			
Patient unconscious and/or lacks mental capacity	50/51 (98%)	8064/8659 (93.1%) [86.6% - 96.4%][‡]	NS
Patient will not understand	1/51 (2%)	456/8659 (5.3%) [2.8% - 11.0%]	NS
Other reason	0/51 (0%)	139/8659 (1.6%) [0.8% - 2.5%]	NS

Note that regarding reasons that discussions were not held with families was only reported for four South African families and so these data are not included in the table.
[†] Information only known for 51 South African patients.
[‡] The information in the square brackets in this table is the range of percentages in the different regions of the world outside South Africa for which information was known.

life-sustaining therapies have advanced to the extent that the dying process can be prolonged and lead to unnecessary suffering [5,22,23]. Nevertheless, the frequency of LLST in SA has not been previously comprehensively documented and is not well known amongst the public or doctors. We hypothesized that in resource-limited South African ICUs, the need to free up ICU beds for new admissions would be an important consideration, and that rates of LLST might be higher compared with the global norm. Surprisingly, the opposite was observed. The rate of both withholding and withdrawing was substantially lower than in other countries. In fact, SA reported the lowest rate of all world regions, albeit from only one ICU [2]. Correspondingly, the rate of failed CPR prior to death was the highest in the world, more than double that reported in Latin America and Southern Europe, the regions with the next highest rates, and six times that of the rest of Europe and North America [2]. The reason for this may well be due to the fact that there is a lack of guidance with regard to the use of do-not-resuscitate order in SA [24].

The reasons for all these differences documented require further examination. We may speculate that in SA, because ICU beds are a severely restricted resource, as described previously, admission triage processes are necessarily very strict, resulting in a disproportionate number of admissions of substantially younger patients, with little chronic comorbidity and with reversible acute conditions, as has been shown in other studies, including others from SA [11-13]. The presence of some of these factors is substantiated by our data, indicating that a

larger proportion of patients did not present with many of the clinical factors, such as multiple comorbidities and chronic disease that trigger LLST in other regions, resulting in lower rates of withholding and withdrawal. While these factors may have contributed to the differences seen, they certainly cannot fully explain the magnitude of differences reported.

A previous survey performed in Asia showed that ICU physicians in low-middle-income countries (LMIC) were less likely to limit mechanical ventilation, vasopressors, inotropes, tracheostomy, and hemodialysis than those from high-income regions, and more likely to provide CPR at the end of life [25]. The authors attributed this difference to a relative lack of professional guidance, legal support, and a lack of physician and public education on the benefits of appropriate and humane end-of-life care. A later prospective, worldwide audit examining withholding/withdrawing rates, confirmed this impression, and reported that decisions to withhold/withdraw therapy were significantly less frequent in LMIC [26]. Cultural and religious beliefs are also likely to contribute to end-of-life care practice, although our limited data did not specifically identify such an influence in our South African cohort.

Interestingly, the need for an ICU bed was reported as only rarely being a consideration for LLST, and never the primary consideration. This latter observation corresponds with the international consensus view that end-of-life decisions should be made primarily based on individual patient goals, preferences, and likely benefit [5], rather than the consideration of distributive justice [14]. While many of the explanatory factors discussed above may be relevant, the substantial differences in withholding and withdrawal practice in SA are striking, deserving future investigation.

While withdrawal and withholding of therapy are generally considered to be equivalent forms of LLST from an ethical standpoint in many regions of the world and underlies general global consensus, it is not universal [5,27]. For example, in China they are not seen as ethically equivalent by 74% of ICU physicians [28]. There are also large regional differences in the way they are applied [2]. In our study, both globally and in SA, withholding therapy was more common than withdrawal. The reasons for this, both in SA, and internationally, may be pragmatic, and in some regions possibly related to cultural, religious, and personal beliefs, professional guidance, or local legal and legislative requirements [2,21,28].

Ethical uncertainty places a considerable burden on the doctors who make these decisions, even if there is support from the nursing and other medical staff [29]. Our study did indicate, however, that there was considerable consultation amongst staff, which resulted in high levels of agreement amongst medical staff as has been shown previously both in Africa and the rest of the world [4]. In only one patient in the South African ICU was there a documented delay in WH or WD therapy due to disagreement amongst staff, which was not significantly different to the rest of the world. Nevertheless, it may still be advantageous to have a palliative care team assist in the process by participating in joint decisions [30].

As expected, South African patients were younger and this is likely representative of the population characteristics, but possibly also is the result of the need for routine resource-driven admission triage, that may restrict the admission of older patients with chronic co-morbidity and poorer functionality and life expectancy to the ICU [14]. In this regard, age was not reported as a factor determining LLST in SA although it has been recognised as a factor elsewhere [21]. It is gratifying that age alone is generally avoided as a reason to initiate LLST, particularly if the individual is functionally robust [31,32]. As such, withdrawing or withholding therapies should, in this circumstance be the result of a multifactorial decision as demonstrated in the study by Guidet et al. [32], in which the key factors associated with LLST were acute ICU admission, elevation in the Clinical Frailty Scale score, increased age, as well as SOFA score.

Immunological comorbidity (most likely related to the overall incidence of people living with the human immunodeficiency virus in SA) was considerably higher in SA than the rest of the world [33], suggesting that triage practices do not appear to limit access of these patients to the ICU. Cardiovascular diseases were less common underlying comorbidities in SA, which may be a result of the younger age of admitted patients, but also to the fact that this hospital has separate cardiac and cardiothoracic ICUs.

Our data demonstrated that patients' self-expressed wishes were seldom known, which is understandable given that the majority in whom there was LLST, were already unconscious and lacked mental capacity to make their wishes known.

A notable concern was the lack of known patient preferences whether obtained from the family or the use of an advance directive. In fact, no advance directives were available for South African patients. While only available on average in 10.8% of patients globally, some regions, such as North America, have made substantial progress in achieving rates of up to 50% [4]. The low rate of advance directive availability in South African patients is not surprising since they are not legally binding in South African law [34]. This is in contrast to countries such as the United States, where the Self Determination Act provides patients with the information about their right to execute advanced directives (The Patient Self Determination Act, Pub. L. No. 101–508, §§ 4206 & 4751, 104 Stat. 1388 (codified at 42 USC §§ 1395 cc(f), 1396a (w) (1994)). The findings of the current study support the urgent need for legal recognition of advance directives in SA and for public education regarding the meaning and value of them. Internationally, active SDP was rare and there were no cases in SA; this finding aligns with the legal status quo in SA where euthanasia is illegal, but this is currently the subject of considerable legal and ethical debate [35].

As opposed to other studies [5], we did not demonstrate that religion or religiosity amongst doctors had any measurable impact on decision-making, although the number of doctors in each religious group was small, and a real effect cannot be excluded.

In our cohort, only one patient with LLST survived, which contrasts with the global cohort where 16.7% of 12,732 patients with LLST survived. However, this was similar to a study comparing one ICU each in the USA, UK and SA (Cape Town), in which withdrawing therapy was associated with a significantly higher mortality in the South African ICU compared to the others ($p < 0.001$) [9]. It can be speculated that in regions where there is more awareness and acceptance of LLST by doctors and the public, that LLST may occur more frequently and earlier in the disease process. This change over time was seen in Europe between 1999 and 2016 and was associated with greater survival rates in all categories of patients who had LLST during the later period [17].

However, interestingly, there was a tendency for the median time from ICU admission to first limitation decision to be higher ($p = 0.08$) and the median time from first limitation to death to be shorter in the South African ICU compared with the rest of the world; $p < 0.001$ (Supplementary Table 1). This contrasts with previous studies, in which the time from admission to first LLST was shorter in the South African ICU than in the other ICUs with which the unit was compared [9]. Differences found when comparing the two South African ICUs, could be due to differing types of ICUs, different case mixes due to different resource constraints, and differences in admission criteria, as described previously [9]. In this regard it was noted in the study that included the Cape Town ICU [9] that increases in admissions over the festive season occurred for trauma-related events, which were associated with increased withdrawal events, while the Johannesburg ICU did not admit trauma cases during its study period.

It is important that LLST decisions should always be based on an ethical framework, such as that devised by the General Medical Council in the United Kingdom [35], which issued end-of-life guidance, outlining the ethical principles critical to decision-making in these circumstances [36]. While the circumstances in which LLST should be considered appear self-evident, they are not generally taught in medical school or in hospitals [30,37], especially in SA.

The strength of the study is that it is the first comprehensive,

prospective investigation of the practice of EOL care in SA, with a high number of included cases, uniformly collected data, and a comprehensive follow-up period. In addition, the study contrasts the findings in SA with the centres that participated around the world. However, this study also has several limitations. First, the study reports practice in only one South African unit, and other global regions were not studied equally, since our attempts to recruit representative sites in each region were unsuccessful. In addition, the South African ICU included was in the public, rather than private sector, and as such the findings may not be generalisable to all South African ICUs; however, this ICU was the only one in the country that had agreed to participate. Second, unavailable data did not allow full examination of the physician's knowledge of patient preferences, an important aspect of decision-making. Third, it was not always possible to record all the underlying causes of the differences in practice observed. One example is that since the availability of beds impacts on the case-mix, this makes much of the ICU data difficult to compare from unit to unit without correcting for these differences. This has been noted previously by others who also indicated that this fact is seldom discussed or even mentioned as a limitation [11]. Lastly, there may be some bias in the way the data was entered into the database, if those entering the data felt obliged to answer in a particular way and were unaware of their own subconscious influences. However, a strength of the South African part of the study, was that the person entering the data was always a senior ICU physician.

In conclusion, LLST occurs commonly in SA, but at a lower rate than in the rest of the world. There is a high level of agreement with decision-making between ICU doctors and nurses, and other treating doctors. The rate of withholding and withdrawing LLST in SA was much lower than the global average and the reasons for this difference require further investigation. While the circumstances in which LLST should be considered appear self-evident, they are not generally taught in medical school or in hospitals, especially in SA. Further education surrounding these issues should be an important part of the SA medical curriculum. Enhancing public awareness and understanding of the use of advance directives may also be considered as part of a wider program to raise public awareness of the need for EOL planning.

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CRediT authorship contribution statement

Charles Feldman: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Gavin M. Joynt:** Writing – review & editing. **Spyros D. Mentzelopoulos:** Writing – review & editing. **Charles L. Sprung:** Writing – review & editing. **Alexander Avidan:** Writing – review & editing. **Guy A. Richards:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154797.

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