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Editorial

The truism of 'life limiting illness' in ICU

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Intensive care can result in significant physical, psychological, and emotional burdens on both patients and their next-of-kin.[1] The risk of negative outcomes from ICU treatment may be greater in patients who have substantial pre-existing co-morbidities. Accounting for uncertainties in the patient's prognosis, clinicians must balance the utility and harm of invasive ICU treatments, acknowledging that these have the ability to prolong suffering, whilst potentially providing limited benefit. Furthermore, the impact of critical illness means that many ICU 'survivors' transition to poor health outcomes after discharge, with significant additional mortality in the initial weeks and months after leaving the hospital.[2] The concept of a time-limited trial in ICU has been proposed as a practical approach to establish the goals of ICU care when the long-term outcomes and overall benefits of aggressive interventions are uncertain.[3,4] A time-limited trial is typically suitable for patients with reduced life expectancy or physiological reserve, and for those whose ICU treatment cannot be clearly categorised as beneficial or non-beneficial.[3]

In this issue of *Critical Care and Resuscitation*, Wagner and colleagues investigated the prevalence and long-term outcomes of patients with life-limiting illnesses (LLI), defined as the presence of one or more APACHE-II or APACHE-III chronic organ insufficiency, frailty, or metastatic cancer, admitted to ICUs across Australia and New Zealand.[5] The authors found that more than one in five patients had at least one LLI, which were all independently and cumulatively associated with an increased likelihood of death. Although the authors found that patients with LLI were more likely to have treatment limitations at the time of ICU admission, these patients also had longer ICU and hospital stays. The study adds to the growing body of literature identifying the importance of LLI on admission to hospitals and in demonstrating their association with poorer long-term outcomes. Significant strengths of the study were the considerable sample size (n = 566,260) of patients included, and the precise associations demonstrated between each LLI and survival time, which were concordant across sensitivity analyses.

Perhaps the most notable finding of this study was the worst outcomes observed for those patients with metastatic cancer and higher frailty degree, with particularly high mortality in patients exhibiting both factors. In Wagner and colleagues' study cohort,[5] more than one-quarter of these patients with LLI had higher degrees of frailty (clinical frailty scale [CFS] score ≥6). This is in keeping with recent studies, which have found significantly worse health outcomes in these higher-frailty degree patients,[6] including a longer stay in ICU and hospital, non-home discharge, complications (delirium, pressure injuries), and mortality.[7] The grouping together by the authors of CFS 4–5 as 'pre-frail' may be questioned, as the iteration of the CFS used in the registry for the study period defines CFS 5 patients as living with mild frailty, and the most recent update to the CFS now categorises *CFS 4* patients as already 'living with very mild frailty'.[8] It is telling, however, that these lesser degrees of frailty still had a greater impact on long-term mortality than did any other life-limiting illness diagnosis apart from metastatic cancer, cirrhotic liver disease, or, indeed, advanced frailty (CFS 6–8), reflecting prior research findings.[9,10] These observations stress the importance of identifying frailty early, and the role of multidisciplinary decision-making to develop individualised management strategies for these high-risk patients.

This study, however, does raise important questions that will require further work to address. A significant proportion of the excess mortality observed in patients with frailty and metastatic cancer was early and within the index hospitalisation or even the index ICU admission. Patients with LLI had double the ICU mortality, and more than double the hospital mortality than patients without LLI, with this early divergence in survival explaining much of the longer-term difference found between groups. Further research is thus required to understand better factors contributing to post-discharge mortality in ICU survivors with LLI.

Although nearly 30% of patients had an LLI, only 17% of these patients had a treatment limitation at ICU admission; many others would likely have had either new or revised goals of care documented in the ICU. Identifying characteristics linked to poorer outcomes can facilitate shared decision-making discussions about options for treatment and help align such treatment with patients' goals and values. Prior research has identified this as an area for improvement. For example, a recent study demonstrated that only 50% of patients with frailty older than 80 years had early goals of care documentation within 72 h from admission to a medical ward.[11] Wagner and colleagues[5] have extended our understanding of this vulnerable patient cohort, serving as an important reminder for physicians to be more proactive in establishing timely goals of care documentation to avoid burdensome treatment, improve

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clinical outcomes, and decrease non-beneficial healthcare resource expenditure.

Wagner and colleagues[5] also found that patients with organ failure LLIs, apart from chronic liver disease, had relatively better survival than those without LLI. Although this is an important finding, this finding should be interpreted cautiously as there is significant heterogeneity in the clinical presentations of such patients.[12] Furthermore, the authors did not investigate the cumulative effect of these organ failure LLIs with frailty. This may have provided more insights into how frailty interacts with these co-morbidities. Although it is evident that frailty was independently linked to decreased long-term survival in patients who were admitted to the ICU due to a worsening of chronic obstructive pulmonary disease,[10] it is unclear if the same interaction exists with other organ failure LLIs.

This study also observed that patients with LLI less frequently received mechanical ventilation. While the authors did not report the duration of mechanical ventilation, prior research has shown patients with frailty receive mechanical ventilation for longer and are less likely to be extubated,[13] resulting in death, non-home discharge, failure of extubation, and requirements for tracheostomy.[14] These mechanically ventilated patients are then also more likely to go on to develop persistent critical illness, with attendant significantly increased ICU health care consumption and mortality.[15] Therefore, a strategy minimising invasive mechanical ventilation with more utilisation of non-invasive oxygenation strategies,[16,17] for patients with LLI and frailty may be beneficial. The landscape of organ support provision would appear more complex, however, as patients with LLI more frequently received renal replacement and vasopressor therapies than those without LLI. What underpins this difference in organ support in these patients with LLI, and how can we best ensure the maximal potential benefit with the least amount of patient burden?

'Time-limited' ICU trials as a default management strategy for patients with advanced medical illnesses have been shown in smaller studies to reduce length of stay and invasive procedures, without affecting the overall hospital mortality or family satisfaction with ICU care.[4] The F.R.A.I.L. screening checklist (Functional impairment, Recurrent hospitalisations, Advanced malignancy or chronic diseases, Irreversible organ failure and Long hospital stay) has been proposed as a prompt to admit critically ill patients who might benefit from a time-limited trial in the ICU.[18] Any patients with a F.R.A.I.L score >0, by definition have LLI.[18] A small study of 320 older patients aged 70 years and over with COVID-19 found that the F.R.A.I.L. checklist identified patients who benefited from a time-limited trial in ICU and correlated well with the CFS (Spearman's rho 0.53; $p < 0.001$).[19] However, the F.R.A.I.L. screening checklist has not yet been validated on a larger scale as a criterion for ICU admissions or for establishing timely ICU goals for patients who might benefit from time-limited ICU trials. Furthermore, although patients with LLI may survive hospital discharge, a large proportion will have poorer functional status and a higher risk of death. Tools such as this may help with care planning and ongoing goal-concordant care.

Finally, like all research utilising data from critical care audit databases, extrapolating results to different environments necessitates knowing how critical care services are organised, the criteria for admitting patients, and the general societal attitudes toward critical care. Therefore, the observed rates of LLI and its correlation with outcomes in Australia and New Zealand might not be applicable in other contexts. Moreover, due to the retrospective design of the study, the relationships identified should be viewed as correlations, not as evidence of causation.

To conclude, Wagner and colleagues[5] have answered important questions in identifying the likely impact of LLI on critically ill patients, in both the short and long term. It is increasingly clear that a 'one-size-fits-all' approach to caring for patients with LLI in ICU is not appropriate. This study reminds us as clinicians to be advocates for our patients with LLI when considering ICU admission, and what we do for them once admitted. Further research examining possible models and criteria for time-limited ICU trials for these high-risk patient groups may be a way forward in ensuring goal-concordant ICU care and allowing the best possible outcomes with the least possible burden.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Cheung EH-L, Cheung JC-H, Yip Y-Y. Raising awareness for time-limited trial discussion upon ICU triage and admission. Intensive Care Med 2022;48(2):240–1. https://doi.org/10.1007/s00134-021-06590-0.
[2] Lone NI, Gillies MA, Haddow C, et al. Five-year mortality and hospital costs associated with surviving intensive care. Am J Respir Crit Care Med 2016;194(2):198–208. https://doi.org/10.1164/rccm.201511-2234OC (In eng).
[3] Vink EE, Azoulay E, Caplan A, Kompanje EJO, Bakker J. Time-limited trial of intensive care treatment: an overview of current literature. Intensive Care Med 2018;44(9):1369–77. https://doi.org/10.1007/s00134-018-5339-x.
[4] Chang DW, Neville TH, Parrish J, et al. Evaluation of time-limited trials among critically ill patients with advanced medical illnesses and reduction of nonbeneficial ICU treatments. JAMA Intern Med 2021;181(6):786–94. https://doi.org/10.1001/jamainternmed.2021.1000.
[5] Wagner Ko N, Milnes S, Secombe P, Philpot S, Pilcher D. Prevalence and long-term outcomes of patients with life-limiting illness admitted to intensive care units in Australia and New Zealand. Critical Care and Resuscitation 2024. https://doi.org/10.1016/j.ccrj.2024.02.001.
[6] Darvall JN, Bellomo R, Paul E, et al. Routine frailty screening in critical illness: a population-based cohort study in Australia and New Zealand. Chest 2021;160(4):1292–303. https://doi.org/10.1016/j.chest.2021.05.049.
[7] Subramaniam A, Ueno R, Tiruvoipati R, et al. Comparing the clinical frailty scale and an international classification of diseases-10 modified frailty index in predicting long-term survival in critically ill patients. Crit Care Explor 2022;4(10):e0777. https://doi.org/10.1097/CCE.0000000000000777.
[8] Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. Can Geriatr J 2020;23(3):210–5. https://doi.org/10.5770/cgj.23.463 (In eng).
[9] Alamgeer M, Ling RR, Ueno R, et al. Frailty and long-term survival among patients in Australian intensive care units with metastatic cancer (FRAIL-CANCER study): a retrospective registry-based cohort study. Lancet Healthy Longev 2023;4(12):e675–84. https://doi.org/10.1016/S2666-7568(23)00209-X.
[10] Donnan MT, Bihari S, Subramaniam A, Dabscheck EJ, Riley B, Pilcher DV. The long-term impact of frailty after an intensive care unit admission due to chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis 2024;11(1):83–94. https://doi.org/10.15326/jcopdf.2023.0453.
[11] Subramaniam A, Tiruvoipati R, Green C, et al. Frailty status, timely goals of care documentation and clinical outcomes in older hospitalised medical patients. Intern Med J 2021;51(12):2078–86. https://doi.org/10.1111/imj.15032.
[12] Stewart J, Bradley J, Smith S, et al. Do critical illness survivors with multimorbidity need a different model of care? Crit Care 2023;27(1):485. https://doi.org/10.1186/s13054-023-04770-6.
[13] Okahara S, Subramaniam A, Darvall JN, Ueno R, Bailey M, Pilcher DV. The relationship between frailty and mechanical ventilation: a population-based cohort study. Ann Am Thorac Soc 2022;19(2):264–71. https://doi.org/10.1513/AnnalsATS.202102-178OC.
[14] Fernando SM, McIsaac DI, Rochwerg B, et al. Frailty and invasive mechanical ventilation: association with outcomes, extubation failure, and tracheostomy.

Intensive Care Med 2019;45(12):1742–52. https://doi.org/10.1007/s00134-019-05795-8 (In eng).
[15] Darvall JN, Bellomo R, Bailey M, Young PJ, Rockwood K, Pilcher D. Impact of frailty on persistent critical illness: a population-based cohort study. Intensive Care Med 2022;48(3):343–51. https://doi.org/10.1007/s00134-022-06617-0 (In eng).
[16] Ferreyro BL, Angriman F, Munshi L, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. JAMA 2020;324(1):57–67. https://doi.org/10.1001/jama.2020.9524 (In eng).
[17] Pitre T, Zeraatkar D, Kachkovski GV, et al. Noninvasive oxygenation strategies in adult patients with acute hypoxemic respiratory failure: a systematic review and network meta-analysis. Chest 2023;164(4):913–28. https://doi.org/10.1016/j.chest.2023.04.022 (In eng).
[18] Cheung EH, Cheung JC, Yip YY. Raising awareness for time-limited trial discussion upon ICU triage and admission. Intensive Care Med 2022;48(2):240–1. https://doi.org/10.1007/s00134-021-06590-0.
[19] Wernly B, Flaatten H, Leaver S, et al. The clinical frailty scale, but not the FRAIL checklist is associated with mortality in old critically ill patients with COVID-19. Crit Care 2023;27(1):101. https://doi.org/10.1186/s13054-023-04398-6.

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