# The association between the decision to withdraw life sustaining therapy and patient mortality in UK intensive care units

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**ABSTRACT**

***Objective**:* Differences in decisions to limit life sustaining therapy are often supported by perceptions that patients receive unnecessary and expensive treatment which provide negligible survival benefit. However, the assumption behind those beliefs – i.e., that life sustaining therapy provides no significant marginal survival benefit - remains unproven. Our objective was to quantify the effects of variations in decisions to withdraw or withhold life sustaining treatment (DWLST) on 180-day mortality in critically ill patients

***Design**:* Retrospective observational cohort study of a national clinical database

**Setting**: Adult Intensive Care Units (ICUs) participating in the Intensive Care National Audit and Research Centre Case Mix Programme in the United Kingdom.

***Patients***: Adult patients admitted to general ICUs between 1 April 2009 and 31 March 2016.

***Measurements and main results*:** During the study period, 795,721 patients were admitted to 247 ICUs across the UK. A DWLST was made for 92,327 (11.6%) patients. A multilevel model approach was used to estimate ICU-level practice variation. The ICU-level practice variation was then used as an instrument to measure the effects of DWLST on 180-day mortality. The marginal population was estimated to be 5.9% of the total cohort. A DWLST was associated with a marginal increase in 180-day mortality of 25.6% (95%CI 23.2% to 27.9%).

***Conclusions:*** DWLST in critically ill adults in the UK was associated with increased 180-day mortality in the marginal patients. The increased mortality from a DWLST in the marginal patient may be informative when establishing patients’ preferences and evaluating the cost-effectiveness of intensive treatments.

Keywords: end of life; healthcare quality; variation; intensive care units

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## Introduction

The decision to withhold or withdraw life sustaining treatment (DWLST) occurs relatively frequently in Intensive Care Units (ICUs) (1). More than 90% of patients facing this choice in ICU settings lack the capacity to make such a decision and their preferences are elicited from advance directives or surrogate decision-makers (2). Patients' lack of capacity impacts shared decision-making, and often a DWLST represents the physician's assessment of prognosis and assumptions of patient preferences (3). A major limitation of this process is that the physician's prognostic estimate is often made with incomplete information, and influenced by many factors such psychological heuristics, prior experience and cognitive biases. Even in environments with significant quantities of complex data like the ICU, there are wide margins of uncertainty and the discriminative accuracy of physician predictions for survival is modest (3). While attempting to find the balance between providing life-saving treatment and preventing futile care in the face of such uncertainty, the DWLST may disproportionately represent a physician's prognostic pessimism more than reliable prognostic estimates. As a result, a DWLST may contribute to higher mortality for some patients beyond that attributed to disease or patient characteristics.

A DWLST is commonly associated with a burden of co-morbidity and severe acute illness, yet prior studies have found considerable variation in DWLST between countries and between

ICUs within countries (4-6). A study by Quill and colleagues in the US found a six-fold increase in DWLST between ICUs after accounting for patient and ICU characteristics (7). In this study, ICUs with a higher propensity for DWLST had a higher standardised mortality, suggesting an association between high DWLST-use and poorer clinical outcomes (7). Studies in Europe describe wide variations in DWLST in ICUs but have not explored the causal relationship between DWLST and survivorship (8, 9). Predictions of ICU survivorship are notoriously unreliable and may be contingent on the intensity of treatments provided. In a study across 84 countries, up to one-third of patients with a DWLST left the hospital alive (4). In the US, severely ill patients had higher post-admission survival when admitted to hospitals with high treatment intensity and had higher 100-day survival after receiving care that might have been considered ineffective (10) (11).

The association between higher DWLST and higher mortality described in prior studies overestimates the causal effects of DWLST because many patients receiving such a decision are likely to die with or without it (10, 12, 13). There are incompletely measured patient, physician and institutional characteristics that are correlated with both the DWLST and mortality.  One such factor may be prognostic pessimism. Patients admitted to ICUs that are generally more pessimistic about patient's survival prospects are more likely to receive an inappropriate DWLST. We sought to measure the ICU-level variation of DWLST and estimate its incremental effects on 180-day mortality by using an instrumental variable approach to account for unmeasured confounding.

## Methods

*Patients and variables*

Eligible patients were admitted to the ICU between 1 April 2009 and 31 March 2016. Patients younger than 16 years were excluded. For each ICU admission, data was available on age, gender, ethnicity, co-morbidities, length of ICU and hospital stay and outcome. Socio-economic status was described using the Index of Multiple Deprivation and severity of illness by the ICNARC score (14, 15). ICU characteristics included the academic affiliation, speciality status, number of ICU beds and ICU caseload volume. The primary analysis included only the final admission to the ICU. We assumed that for patients that were readmitted, the DWLST would likely occur in the last admission and that restricting the analysis to the first admission would likely underestimate the incidence of DWLST.

*Exposure Variable*

A decision to limit life sustaining therapy included either the withholding or the withdrawal of treatment. Withholding treatment was defined as not initiating therapies that would otherwise be clinically indicated were it perceived to be beneficial to the patient. Withdrawal was defined as the scenario where all potential curative therapies are discontinued, and symptomatic care initiated.

*Outcome variable*

The primary outcome was 180-day mortality. The secondary outcome was 90-day mortality.

*Data source*

The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (16). This study used a nationally representative sample of 247 UK ICUs from the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Program (CMP) database to describe the epidemiology of ICU DWLST (17). The CMP is a voluntary subscription-based program used for benchmarking and quality improvement. The CMP-specified data is recorded prospectively and abstracted by trained data collectors (17). The use of this data has been approved for the Case Mix Programme by the Confidentiality Advisory Group (CAG) within the Health Research Authority (HRA) – Approval number: Patient Information Advisory Group 2-10[f]/2005.

*Statistical Analysis*

Chi-squared and *t* tests were used to assess the relationship between patient characteristics and DWLST. We then specified a multilevel mixed-effects logistic regression model to assess decisions to limit life sustaining therapy rates. The multilevel mixed-effects model allows us to assign ICU-level random intercepts which is analogous to predicted residuals in the ordinary least squares model (18). A more detailed description is provided in the Appendix.

*Instrumental variable*

The ICU-level random effect from the multilevel analysis was used as the instrument. The random effect represents that component of DWLST not explained by observable patient or ICU characteristics and can be thought of prognostic pessimism that manifests as practice variation. An ICU-level instrument is able to estimate the causal effect of ICU-level variation in DWLST. The three conditions for a valid instrument are (a) it must be correlated with the endogenous treatment variable; (b) must have no direct effect on the outcome other than through the treatment; and (c) should be independent of unmeasured confounders of the treatment-outcome relationship accounting for observed confounders. Details of the conceptual description of the instrument and a more detailed statistical plan are included in the Appendix.

*Interpreting the results of the instrumental variable model*

The results of the instrumental variable describe the effects in the marginal population and not the average treatment effect described by standard regression techniques. The marginal population can be considered in the following paradigm: some patients are very unwell and would have had a DWLST irrespective of which ICU they were treated in; another proportion of patients are well and never receive a DWLST. The instrumental variable approach only estimates the treatment effect for the patients that do not fall into either of these groups (i.e., those patients who are unwell yet receive a DWLST). The treatment measured by the instrumental variable approach only refers to the subgroup of patients for whom the treatment was determined by the instrument.

The method described by Newhouse and McClellan was used to estimate the relative size of the marginal population (19). In this approach, the subgroup of patients for which the instrumental variable analysis applies can be estimated by differences in the average rate of DWSLT in the two patient populations stratified by the mean of the instrument (20). In a multilevel model, the mean of the random intercept is zero. Groups were stratified by those ICUs with positive versus negative random intercepts.

*Subgroup and Sensitivity analysis*

We considered the possibility that there may be substantial practice variation between specialist and general ICUs. We conducted a subgroup analysis of DWLST in patients admitted to general ICUs. Additionally, variation involving surgical patients may, in part, represent differences in surgical practice. We conducted a subgroup analysis restricted only to medical patients. The common mechanism for a DWLST would be the patient's burden of co-morbidity, the severity of the acute illness at presentation and ICU trajectory over time. An early DWLST that does not include ICU trajectory may be associated with a higher mortality. We explored the potential effects of early DWLST by performing an analysis of DWLST taken within 48 hours of ICU admission.

The primary analysis considered withholding treatment and withdrawing treatment to be equivalent. Whilst there may be broad consensus on this approach, there are differences in the way these decisions are operationalised (1, 21). Decisions to withdraw therapy requires a written medical order and is likely to be well documented. In contrast, decisions to withhold treatments reflect the absence of a treatment and may be less consistently recorded. It is possible that these differences in the way withholding is recorded may manifest as differences in institutional rates of DWLST. To address this possibility, we undertook an analysis restricted to withdrawal only.

A general critique of instrumental variable analysis is the potential for inconsistent estimates and lower efficiency induced by weak instruments. We performed an inverse-probability weighed regression analysis (IPWRA) to establish the consistency of the estimates across analytic approaches. The IPWRA is a doubly robust method that combines reweighting with regression analysis. The results are reliable if either the propensity model or the regression analysis has to be correctly specified. The IPWRA assumes that all the covariates for either the reweighting procedure or the regression analysis are fully measurable, which is a key difference with the instrumental variable approach.

## RESULTS

### Description of patients and ICUs

There were 795,721 patients admitted to 247 ICUs between 1 April 2009 – 31 March 2016. A DWLST was made for 92,327 (11.6 %) patients. A total of 125/247 (50.6%) of ICUS were above this rate of DWLST. The patient and ICU characteristics are described in Table 1 and Table 2 respectively. On average, patients who received DWLST decisions were older, with a higher illness acuity and more comorbidities. Surgical patients were less likely to have a DWLST compared with medical patients (OR 0.22, 95% CI 0.22-0.22, p<0.001). Patients receiving a DWLST were more likely to reside in a nursing home prior to ICU admission (OR 1.80, 95% CI 1.68-1.84, p<0.001) and more likely to have been readmitted to the ICU during the same hospitalization (OR 1.22 95% CI 1.19-1.25, p<0.001) (Table 1). In unadjusted analyses, patients with the DWSLT compared with those patients with no DWLST had longer ICU stays (mean ICU length of stay in hours: 139.9 hours for DWLST patients vs 105.1 for patients without DWLST; absolute difference 34.8 hours 95%CI 33.5 to 36.1, p<0.001), but had a shorter total hospital length of stay in days (mean hospital stay in days: 12.1 for DWLST patients vs 21.3 for no DWLST patients; absolute difference 9.2, 95% CI 9.0 to 9.4 , p<0.001). Compared with an ICU of less than 10 beds, we found lower odds for DWLST for patients admitted to ICUs with 10 to 14 beds (OR 0.91, 95%CI 0.89 to 0.93), 15 to 19 beds (OR 0.92 95% CI 0.90 to 0.93) and 20 or more beds (OR 0.75 95% CI 0.74 to 0.77). Compared with a general ICU, patients in a cardiac ICU (OR 0.25, 95% CI 0.23-26, p<001), neuro-ICU (OR 0.47, 95% CI 0.45-0.50, p<001) and a stand-alone High Dependency Unit (HDU) (OR 0.45, 95% CI

0.45-0.47, p<0.001) had significantly lower odds of a DWLST (Table 2). Details of the geographic variation and annual trends in DWLST are included in the Appendix (eTable1).

*Variation in DWLST between ICUs*

The results of the multilevel logistic model for DWLST are described in Table 3 and in the appendix. Figure 1 shows the Empirical Bayes estimates of the ICU-effect after controlling for patient and ICU characteristics. ICUs on the left of the graph have a lower use of DWLST and ICUs to the right have a higher use of DWLST than would be explained by measured patient and ICU characteristics. The median odds ratio was 1.78 (95%CI 1.69-1.90) and suggests significant ICU-level variation in DWLST (22).

*Instrumental variable analysis*

An instrumental variable analysis was undertaken to determine the relationship between the DWLST and 180-day and 90-day mortality. The instrument used was the ICU-level variation in DWLST derived from the multilevel model. Following the method of Newhouse and colleagues, the marginal population was estimated to be 5.9%(19). This means that for about 5.9% of patients, the DWLST was influenced by the ICU in which patient was care for (eTable 5).

In the instrumental variable analysis adjusted for patient characteristics, receiving a DWLST was associated with a significantly higher 180-day and 90-day mortality compared with no DWLST. The absolute risk difference of a DWLST was an increase of 25.6% (95%CI 23.2% to 27.9%) on 180-day mortality and 15.8% (95% CI 13.3% to 18.1%) on 90-day mortality. Details of these analyses are included in the supplement (eTable 5).

An instrumental variable approach was justified by significant endogeneity. The Durbin score and Wu-Hausman tests compare the standard regression model with the instrumental variable model(23).The Durbin score was 541 (p<0.001) and the Wu-Hausman was 557 (p<0.001). Tests for weak instruments were performed. The Montiel-Pflueger robust weak instrument test effective F-statistic was 12,015, substantially higher than the critical value of 37 (tau=5%), suggesting a strong instrument. One of the conditions for instrument validity is that there should be no mutual confounders between the instrument and the outcome. Although this cannot be directly proven, it can be inferred by covariate balance across strata of the instrument. The balance of measured covariates across strata assumes the same for unmeasured confounders (eTable 6)(19).

*Subgroup and sensitivity analyses*

A sub-group analysis of DWLST in patients admitted to general ICUs was associated with a marginal increase in 180-day mortality of 49.0% (95% CI 47.5 to 50.7, p<0.001) and a subgroup analysis of medical patients was associated with a marginal increase in 180-day mortality of 47.8% (95%CI 46.2%-49.3%, p<0.001) (Table 4). Early DWLST was associated with an increased mortality of 47.7% (95%CI 45.6%-50.0%, p<0.001).

Sensitivity analyses demonstrated consistent estimates. Restricting the definition of DWLST to include only withdrawal did not reduce the effect size (Table 4). The IPWRA analysis had a predictably larger average treatment effect (marginal effect on 180-day mortality was 63.0% (95%CI 60.9%-65.0%, p<0.001), because this approach does not account for unmeasured confounding. The details of the sensitivity analyses are included in the Supplement Appendix.

## Discussion

Our study found significant ICU-level variation in DWLST. The marginal patient admitted to an ICU with a high propensity for DWLST had a higher 180-day mortality compared with being treated in an ICU with low use of DWLST (6).

In interpreting our results, it is important to understand that this study does not refer to the average ICU patient but to the marginal patient. The instrumental variable analysis applies only to those patients for whom a DWLST depended on which ICU they were admitted to. This does not translate to specific clinical criteria but rather to a group of patients that would be considered borderline for a DWLST.

The multilevel analysis identified significant variation at the institutional level that is not accounted for by patient characteristics and reflects ICU-level practice variation. Whilst this study did not record patient preferences, it included several variables with a consistent relationship with patient preferences (1). Evidence from previous studies suggests that patients of advanced age, with functional limitations and with multiple co-morbidities are more likely to prefer less aggressive interventions; these preferences are stable over time (1, 7, 24).

There may be several reasons to explain the causal effect of a DWLST on 180-day mortality. Physicians make prognostic estimates with imperfect information and wide margins of uncertainty. A patient admitted to an ICU that is on average optimistic may receive appropriate care where a patient admitted to a pessimistic ICU may receive a DWLST.

Physician pessimism about the effectiveness of various interventions may also manifest in differing choice architecture that influence the outcome of discussions with surrogate decision makers (25, 26). In this setting, the physician attitude has no pathophysiologic effect other than to act through the DWLST to influence the observed outcome. Additionally, the patient with a DWLST is less also likely to receive life-prolonging treatment that might be beneficial during another acute illness (27).

This study has several strengths. First, it includes an institutional-level instrumental variable analysis to account for potential unmeasured confounding. This represents an advance on previous studies that have described the effect of DWLST on the average patient using risk adjustment, which is often confounded by indication and unmeasured variables (4, 28-30). Second, this study includes both decisions to withdraw and withhold life sustaining therapy. Decisions to withhold therapy are often not described in previous studies. Lastly, this is one of the largest nationally representative studies of DWLST and includes 100% of all adult general ICUs in the UK (31).

This study should be interpreted within the context of its limitations. First, it is possible that a DWLST could be inaccurately recorded. To address this, we undertook several sensitivity analyses with different definitions of DWLST. These results were consistent with the primary analysis. Second, we cannot confirm that the instrumental variable approach fully addressed unmeasured confounding (32). The subgroup and sensitivity analyses were performed to address this concern and are supportive of the primary results. The balance of covariates across quintiles of the instrument also suggests the absence of mutual confounders between the instrument and the outcome though this cannot be directly proved. Third, this study does not have data on the quality of life of survivors. Estimates about long term quality of life from other studies have often been confounded and inconsistent (10, 33-36). Most survivors of critical illness are home at 6 months, making 180-day mortality a robust outcome (37). Fourth, this study only included the last ICU introducing potential immortal time bias as patients would have to survive the preceding ICU episodes to receive a DWLST. Importantly, there is likely to be less variation in DWLST on the last ICU readmission for these patients. We therefore believe that this approach is reasonably conservative in estimating variation of DWLST.

**Conclusion**

Variation in DWLST in critically ill patients in the UK is significant. In the small proportion of marginal patients, for whom a DWLST appears discretionary, admitted to ICUs with higher than predicted utilisation of DWLST have higher 180-day and 90-day mortality. This study highlights the potential for more patient-centeredness in making DWLST.

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For more information on the representativeness and quality of these data please contact ICNARC.

Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of ICNARC.

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Figure legend

Figure 1. The ICU-level variation in decisions to limit life sustaining therapy. ICUs on the left, below the reference line, use DWLST less often than predicted by patient characteristics. The ICUs on the right use DWLST more often than predicted by patient characteristics.

Figure 1.



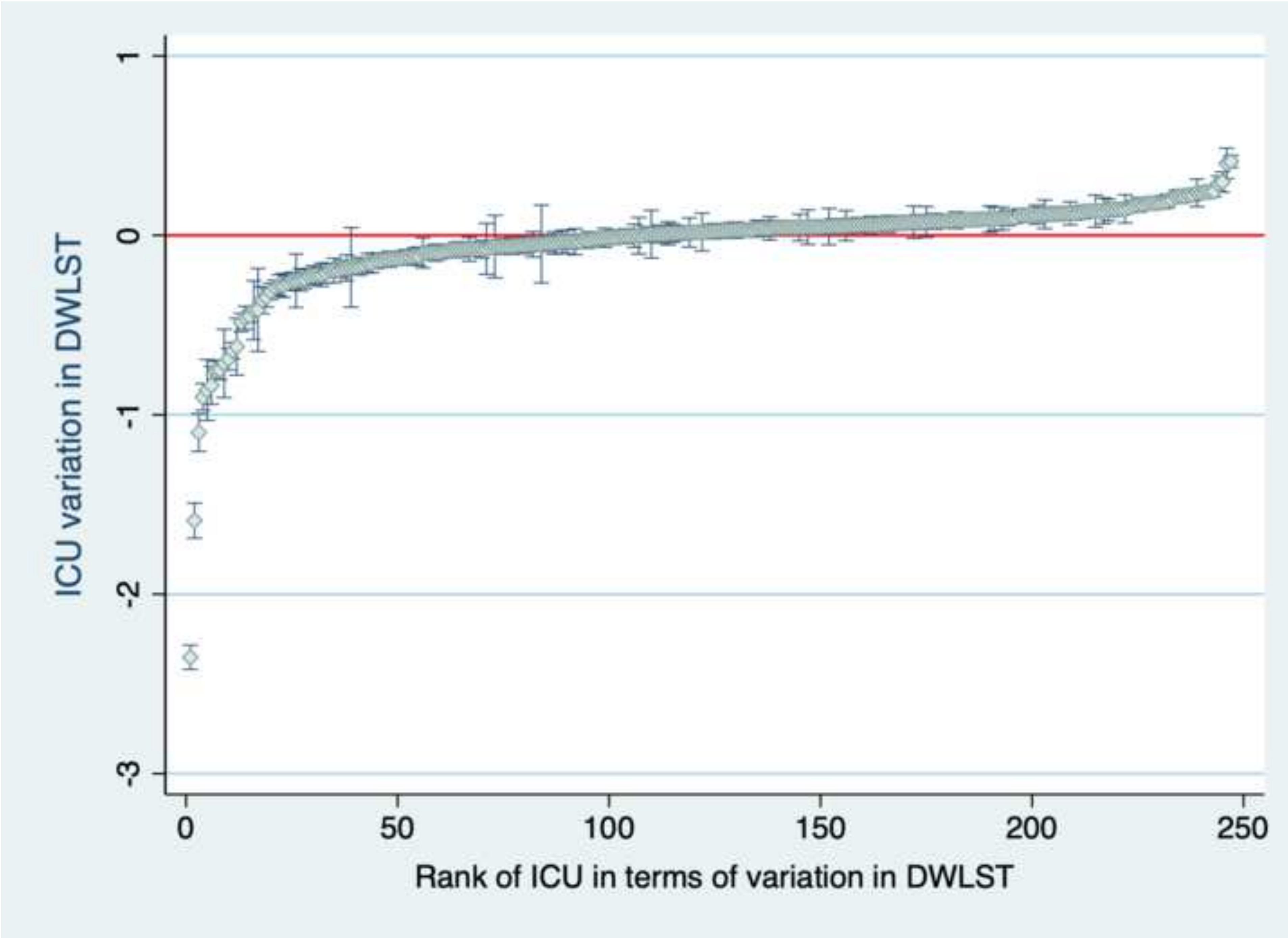
ICU variation in DWLST
1
0
-1
-2
-3
0
50
100
150
200
250
Rank of ICU in terms of variation in DWLST

Table 1

Table 1. Patient characteristics

| Patient characteristics | Patients with no DWLST (%)<br>N= 703394 (88.4%) | Patients with DWLST (%)<br>N= 92327 (11.6%) | p-value | OR | 95% CI |
|---|---|---|---|---|---|
| Age in years | | | | | |
| <48 | 153098(21.8) | 8863(9.6) | - | 1.0 | - |
| 48-60 | 135847(19.3) | 15057(16.3) | <0.001 | 1.91 | 1.86-1.97 |
| 61-69 | 143286(20.4) | 19850(21.5) | <0.001 | 2.39 | 2.33-2.46 |
| 70-77 | 134900(19.2) | 22058(23.9) | <0.001 | 2.82 | 2.75-2.90 |
| >77 | 136263(19.4) | 26499(28.7) | <0.001 | 3.36 | 3.28-3.44 |
| | | | | | |
| Residence prior to Admission | | | | | |
| Home* | 691027(98.2) | 89665(97.1) | | 1.0 | |
| Nursing home** | 10496(1.5) | 2398(2.6) | <0.001 | 1.80 | 1.68-1.84 |
| No fixed address | 1864(0.3) | 261(0.3) | 0.250 | 1.08 | 0.95-1.23 |
| | | | | | |
| Level of dependency prior to admission | | | | | |
| Independent | 550461(78.8) | 58784(64.1) | - | 1.0 | |
| Requires some assistance | 143411(20.5) | 31683(34.6) | <0.001 | 2.07 | 2.04-2.10 |
| Total assistance | 4907(0.7) | 1181(1.3) | <0.001 | 2.25 | 2.11-2.40 |
| | | | | | |
| APACHE II score# | 14.68(0.01) | 22.53(0.02) | <0.001 | 1.16 | 1.16-1.16 |
| ICNARC score# | 14.98(0.01) | 27.27(0.03) | <0.001 | 1.13 | 1.13-1.13 |
| | | | | | |
| Type of patient | | | | | |
| Medical | 347445(49.4) | 75358(81.6) | - | 1.0 | |
| Surgical | 355931(50.6) | 16963(18.4) | <0.001 | 0.22 | 0.22-0.22 |
| | | | | | |
| ICU readmission during the same hospitalization | | | | | |
| No | 665089(94.6) | 86246(93.4) | - | 1.0 | |
| Yes | 38305(5.5) | 6081(6.6) | <0.001 | 1.22 | 1.19-1.25 |
| | | | | | |
| Past medical history | | | | | |
| Cardiac | 11967(1.7) | 2641(2.9) | <0.001 | 1.70 | 1.63-1.78 |
| Respiratory | 13951(2.0) | 4250(4.6) | <0.001 | 2.39 | 2.30-2.47 |
| Renal | 10464(1.5) | 1938(2.1) | <0.001 | 1.42 | 1.35-1.49 |
| Liver | 13935(2.0) | 5196(5.7) | <0.001 | 2.95 | 2.85-3.05 |
| Metastatic Cancer | 22120(3.2) | 3484(3.8) | <0.001 | 1.20 | 1.17-1.25 |
| Hematological malignancy | 11083(1.6) | 3994(4.4) | <0.001 | 2.83 | 2.72-2.93 |
| Immunocompromised | 45222(6.4) | 8004(8.7) | <0.001 | 1.38 | 1.35-1.42 |

Home*= home, work or other non-health related institution, Nursing `home**= nursing home, hospice or other health related institution ; #= mean and standard error

Table 2. ICU characteristics

| ICU characteristics | Patients with no DWLST (%) N= 703394 (88.4%) | Patients with DWLST (%) N= 92,327 (11.6%) | p-value | OR | 95% CI |
|---|---|---|---|---|---|
| ICU beds | | | | | |
| <10 | 179710(25.6) | 26279(28.5) | | 1.0 | |
| 10-14 | 194792(27.7) | 25963(28.1) | <0.001 | 0.91 | 0.89-0.93 |
| 15-19 | 163059(23.2) | 21881(23.7) | <0.001 | 0.92 | 0.90-0.93 |
| >19 | 165833(23.6) | 18204(19.7) | <0.001 | 0.75 | 0.74-0.77 |
| | | | | | |
| ICU volume | | | | | |
| Quartile I | 174510(24.8) | 24927(27.0) | | | |
| Quartile II | 176488(25.1) | 25728(27.9) | 0.032 | 1.02 | 1.00-1.04 |
| Quartile III | 177446(25.2) | 22214(24.1) | <0.001 | 0.88 | 0.86-0.89 |
| Quartile IV | 174950(24.9) | 19458(21.1) | <0.001 | 0.78 | 0.76-0.79 |
| | | | | | |
| Hospital type | | | | | |
| Non-university | 294319(41.8) | 43116(46.7) | - | 1.0 | |
| University affiliated | 112898(16.1) | 15,906(17.2) | <0.001 | 0.96 | 0.94-0.98 |
| University | 296177(42.1) | 33305(36.1) | <0.001 | 0.77 | 0.76-0.78 |
| | | | | | |
| ICU type | | | | | |
| General ICU | 594377(84.5) | 86407(93.6) | - | 1.0 | |
| Cardiac ICU | 44398(6.3) | 1610(1.7) | <0.001 | 0.25 | 0.23-0.26 |
| Neuro-ICU | 24045(3.4) | 1660(1.8) | <0.001 | 0.47 | 0.45-0.50 |
| HDU | 40574(5.8) | 2650(2.9) | <0.001 | 0.45 | 0.45-0.47 |
| | | | | | |

DWLST= Decision to withdraw or withhold life sustain therapy; OR= odds ratio; CI= confidence interval

Table 3

Table 3. Results from mixed-effects logistic model showing odds ratio for decision to limit life sustaining therapy

| **Covariate** | **Odds ratio** | **95% CI** | **p-value** |
|---|---|---|---|
| *Co-morbidities* | | | |
| Severe cardiac disease | 1.04 | 0.99-1.10 | 0.126 |
| Severe respiratory disease | 1.60 | 1.53-1.67 | <0.001 |
| Severe liver disease | 2.27 | 2.18-2.35 | <0.001 |
| Metastatic cancer | 1.53 | 1.47-1.60 | <0.001 |
| Chronic kidney disease | 0.72 | 0.68-0.76 | <0.001 |
| Haematological malignancy | 1.74 | 1.66-1.83 | <0.001 |
| Immunocompromised | 1.22 | 1.18-1.26 | <0.001 |
| *Activities of daily living* | | | |
| Fully independent | Reference | | |
| Some assistance | 1.37 | 1.34-1.40 | <0.001 |
| Fully dependant | 2.16 | 2.01-1.34 | <0.001 |
| Male gender | 0.99 | 0.98-1.01 | 0.422 |
| *Age in cubic splines* | | | |
| Spline 1 | 3.61 | 2.37-5.50 | <0.001 |
| Spline 2 | 7.59 | 5.44-15.19 | <0.001 |
| Spline 3 | 10.63 | 7.44-15.18 | <0.001 |
| Spline 4 | 17.41 | 12.16-18.58 | <0.001 |
| Log (ICNARC score) | 18.19 | 17.81-18.58 | <0.001 |
| *Ethnicity* | | | |
| White | Reference | | |
| Asian | 0.94 | 0.90-0.99 | 0.002 |
| Black | 0.64 | 0.60-0.68 | 0.010 |
| Mixed | 0.80 | 0.70-0.92 | 0.002 |
| Other | 0.97 | 0.89-1.05 | 0.482 |
| Not stated | 1.00 | 0.96-1.06 | 0.781 |
| *ICU type* | | | |
| General | Reference | | |
| Cardiac ICU | 0.57 | 0.41-0.80 | <0.001 |
| Neuro-ICU | 1.67 | 1.12-2.48 | 0.011 |
| High dependency Unit | 0.58 | 0.47-0.72 | <0.001 |

Table 4

Table 4. Absolute risk difference (Marginal effects) from instrumental variable, subgroup and sensitivity analyses for 180-day and 90-day mortality for patients with a DWLST.

| **Analysis, %** | **Absolute risk difference** | **95% CI** | **P value** |
|---|---|---|---|
| *Primary analysis* | | | |
| 180-day mortality | 25.6 | 23.2-27.9 | <0.001 |
| | | | |
| *Secondary analysis* | | | |
| 90-day mortality | 15.7 | 13.4-18.1 | <0.001 |
| | | | |
| *Subgroups* | | | |
| Patients admitted to General ICUs only-180-day mortality | 49.0 | 47.5-50.7 | <0.001 |
| Patients admitted to General ICUs only-90-day mortality | 44.4 | 43.2-45.6 | <0.001 |
| Medical patients only-180-day mortality | 47.8 | 46.2-49.3 | <0.001 |
| Medical patients only-90-day mortality | 42.9 | 41.8-44.1 | <0.001 |
| | | | |
| *Sensitivity analysis* | | | |
| DWLST < 48 hours-180-day mortality | 47.7 | 45.6-50.0 | <0.001 |
| DWLST < 48 hours-90-day mortality | 42.9 | 41.2-44.3 | <0.001 |
| Withdrawal only -180-day mortality | 47.7 | 45.8-49.5 | <0.001 |
| Withdrawal only -90-day mortality | 42.8 | 41.4-44.2 | <0.001 |
| IPWRA – 180 mortality | 63.0 | 60.9-65.0 | <0.001 |
| IPWRA – 90 mortality | 65.0 | 62.28-67.2 | <0.001 |

DWLST= Decision to withdraw or withhold life sustaining therapy; IPWRA =inverse probability regression adjustment