# Abstract

## Purpose

## Methods

## Results

## Conclusions

# Introduction

# Methods

## Search strategy

We searched Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations (1946 to 2022 May 11) and Embase Classic+Embase (1947 to 2022 May 11). The searches combined Medical Subject Headings (MeSH), appropriate controlled vocabulary and keywords for time, death, and withdrawal as utilised in Munshi et al’s 2015 systematic review. The reference lists of all included articles and prior review articles were explored for further inclusions. Clinical experts were consulted to check the included articles for omissions identified through their expertise in the field. Conference abstracts, poster abstracts, letter responses and letters to editors were excluded as tabulated in the PRISMA figure.

## Study selection

Included articles were required to evaluate an adult population in an intensive care environment who underwent withdrawal of life sustaining treatment (WLST). Life sustaining treatment was defined as ventilation (invasive or non-invasive) or haemodynamic support. Measurement from WLST time to death or asystole was necessary for inclusion. Articles that did not evaluate potential predictive factors or models in relation to this measurement were excluded.

Two reviewers (CN, AB) independently reviewed all titles and abstracts identified from the literature searches. Of the articles not excluded in this process full text review was again undertaken by two reviewers. During both of these processes disputes were resolved by a third reviewer (KP).

## Data extraction and quality assessment

Data was extracted from the included articles using customised spreadsheets. Key population characteristics and measurement methods were recorded. The performance metrics of any evaluated predictive factors or models were recorded. Quality assessment was undertaken using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) which was designed to assess the risk of bias (ROB) and applicability of diagnostic and prognostic prediction model studies.

## Data analysis

Given the lack of standardisation of the withdrawal process, heterogenous variable measurement and variation in time to asystole bracketing, data pooling or meta-analysis was not undertaken. Due to this the analysis consists of tabulation of study characteristics and performance metrics with summarisation of the literature as appropriate.

# Results

The initial Ovid MEDLINE and EMBASE via Ovid searches returned 1,145 and 1,969 results respectively to give a total of 2,418 articles to be screened following the removal of duplicates (Fig. 1). Screening of these produced 71 articles for full-text review with an additional paper from reference screening and from expert input. Full-text review produced 23 articles for inclusion in data extraction and analysis.

The populations were relatively evenly split with 11 general populations (1–11) and 11 DCD eligible populations (12–22) with 1 article evaluating a DCD eligible population (23) that was a subset of a previously evaluated general population (1). The median age of the populations ranged between 41 and 66. Mixed ICU populations were the focus of 15 articles (1–4,6,8,10–15,17,19,22) with a total of 5,131 patients. Neurointensive care populations were the focus of 4 articles (5,9,18,20) with a total of 1,181 patients The remaining 3 articles (7,16,21) did not specify the type of ICU that the patients originated from totalling 757 patients.

The majority of articles included death within 60 minutes in their evaluation of variables and/or models with the exception 5 (4,6,10,19,21) that did not evaluate this outcome. The percentage of patients who died within 60 minutes ranged from 44-76% across these articles. Eight articles (7,9,11–13,18,19,22) included death within 120 minutes which ranged from 54-91% of included patients.

Mechanical ventilation was stopped at the point of WLST in all articles with the cessation of vasoactive agents in the majority. The specific process of withdrawal was not typically detailed with only 5 articles (12,14–16,22) specifying that withdrawal of all active treatments was simultaneous.

## Predictive Variables

Seven articles (4,6–8,10,15,19) did not derive or validate any predictive models and instead focused on the identification and/or evaluation of predictive variables. The variables identified using multivariable logistic regression are detailed in Table X.

## Predictive Modelling

The derivation or modification of predictive models occurred in 7 articles (1,7,9,11,12,16,23), the external validation of an existing model was undertaken in 3 articles (14,18,20), and a mixture of both was undertaken in a further 5 articles (2,3,13,17,22). All articles included the evaluation of models for prediction of death within 60 minutes whilst some included evaluation of death within 120 minutes or other ranges. In total 15 unique models were reported with several articles reporting results when refitting these models.

Two of the models evaluated were developed using clinical experience and expert consensus without the reported use of statistical techniques (2,13). These models are unusual as the first published evaluations of their performance are technically external validations as they were both developed without a defined derivation cohort. In the case of the University of Wisconsin DCD Tool (UWDCD) the tool was developed for internal clinical use and was first validated by Lewis et Al. (13) in the hospital area that was already using the tool. The United Network for Organ Sharing Tool (UNOS) was developed based on committee consensus and was validated by DeVita et Al. (2) at five academic hospitals.

Of the remaining models two used classification and regression trees (CART) (2,23), two models used cox regression analysis (9,15) and seven models used other forms of multivariable regression analysis (1,3,7,12,16,17,22). The final 2 models used random survival forests (RSF) (11), and a light gradient boosting machine (22) respectively.

At the point of derivation or modification validation procedures were varied with 5 articles evaluating model performance against the same cohort using for model fitting (2,3,12,13,22), with only 1 of these using cross validation to attempt to mitigate the impact of overfitting (22).

Four models were validated at the point of derivation by splitting the cohort into training and testing sets (1,11,17,23), with a further four validated using an external cohort. One model was validated using a prospective cohort and one was validated using both an external cohort and a prospective cohort .

Reported AUCs for the 60 minute models ranged from 0.45-0.99, sensitivities from 0.39-0.88, specificities from 0.13-0.94, PPVs from 0.34-93 and NPVs from 0.27-0.92.

# Discussion

# Conclusion

# References

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# Appendix

## Appendix 1 – Embase Classic+Embase Search Terms

1. Treatment Withdrawal/
2. ((withdraw\* or withhold\* or limitation\*) adj3 (life support or life sustaining or mechanical\* ventilat\*)).tw.
3. ((withdraw\* or withhold\* or limitation\*) adj2 (treatment\* or therap\*)).tw.
4. treatment cessation\*.tw.
5. or/1-4
6. exp Death/
7. (death or dead or die$1).tw.
8. exp time/
9. exp survival time/
10. time.tw.
11. (6 or 7) and (8 or 9 or 10)
12. (predict\* adj2 death\*).tw.
13. brain death\*.tw.
14. brain stem death\*.tw.
15. cardiac death\*.tw.
16. cardiocirculatory death\*.tw.
17. cardio circulatory death\*.tw.
18. dcd$1.tw.
19. circulatory death\*.tw.
20. clinical death\*.tw.
21. diagnosis of death\*.tw.
22. determination of death\*.tw.
23. or/11-22
24. 5 and 23

## Appendix 2 – Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations Search Terms

1. exp Withholding Treatment/
2. exp life support care/
3. ((withdraw\* or withhold\* or limitation\*) adj3 (life support or life sustaining or mechanical\* ventilat\*)).tw.
4. ((withdraw\* or withhold\* or limitation\*) adj2 (treatment\* or therap\*)).tw.
5. treatment cessation\*.tw.
6. or/1-5
7. exp Death/
8. (death or dead or die$1).tw.
9. exp time/
10. time.tw.
11. (7 or 8) and (9 or 10)
12. (predict\* adj2 death\*).tw.
13. brain death\*.tw.
14. brain stem death\*.tw.
15. cardiac death\*.tw.
16. cardiocirculatory death\*.tw.
17. cardio circulatory death\*.tw.
18. dcd$1.tw.
19. circulatory death\*.tw.
20. clinical death\*.tw.
21. diagnosis of death\*.tw.
22. determination of death\*.tw.
23. or/11-22
24. 6 and 23