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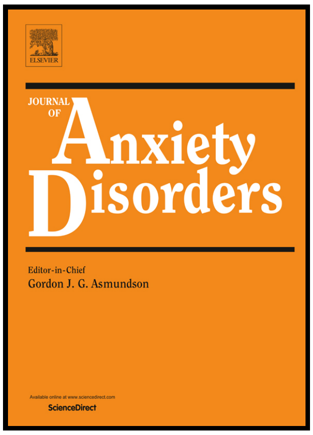

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Using machine learning methods to predict the outcome of psychological therapies for post-traumatic stress disorder: A systematic review

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Abstract

Background:

A number of treatments are available for post-traumatic stress disorder (PTSD), however, there is currently a lack of data-driven treatment selection and adaptation methods for this condition. Machine learning (ML) could potentially help to improve the prediction of treatment outcomes and enable precision mental healthcare in practice.

Objectives:

To systematically review studies that applied ML methods to predict outcomes of psychological therapy for PTSD in adults (e.g., change in symptoms, dropout rate), and evaluate their methodological rigour.

Methods:

This was a pre-registered systematic review (CRD42022325021), which synthesised eligible clinical prediction studies found across four research databases. Risk of bias was assessed using the PROBAST tool. Study methods and findings were narratively synthesized, and adherence to ML best practice evaluated.

Results:

Seventeen studies met the inclusion criteria, including samples derived from experimental and observational study designs. All studies were assessed as having a high risk of bias, notably due to inadequately powered samples and a lack of sample size calculations. Training sample size ranged from *N* < 36 - 397. The studies applied a diverse range of ML methods such as decision trees, ensembling and boosting techniques. Five studies used unsupervised ML methods, while others used supervised ML. There was an inconsistency in the reporting of hyperparameter tuning and cross-validation methods. Only one study performed external validation.

Conclusions:

ML has the potential to advance precision psychotherapy for PTSD, but to enable this, ML methods must be applied with greater adherence to best practice guidelines.

Key words:

Systematic Review; Posttraumatic Stress Disorder; Psychotherapy; Machine Learning.

1. Introduction

Post-traumatic stress disorder (PTSD) is a severe and often chronic mental health problem that can develop following exposure to one or more traumatic events, and is associated with significantly impaired quality of life, increased incidence of physical health problems, co-occurring mental health problems, and suicide (Karatzias et al., 2019; Pacella et al., 2013; Shalev et al., 2017; Yehuda et al., 2015). PTSD affects around 4% of adults worldwide, with higher prevalence rates associated with low income and social deprivation (Fear et al., 2016; Koenen et al., 2017; Ravi et al., 2023). Clinical practice guidelines (CPG) recommend trauma-focussed psychological therapies such as cognitive processing therapy (CPT), prolonged exposure (PE), and eye movement desensitisation and reprocessing (EMDR), as first-line treatments for PTSD (APA, 2017; VA/DoD, 2023; NICE, 2018). Meta-analyses of randomised controlled trials (RCTs) have evidenced that these are currently the most effective forms of psychological therapy for PTSD, and when compared to waitlist controls, pooled effect sizes were large (Jericho et al., 2021; Lewis, Roberts, Andrew, et al., 2020; Mavranezouli et al., 2020). Further, a network meta-analysis (Merz et al., 2019) found that trauma-focussed psychological therapies were equivalent to pharmacological therapy in the short-term and were more effective long-term (Merz et al., 2019), and there is evidence that a majority of patients prefer psychological therapy (including trauma-focussed therapy) to pharmacological therapy (Simiola et al., 2015; Swift et al., 2017).

Despite the availability of efficacious psychological therapies for PTSD, many patients do not respond well to treatment. In a systematic review of RCTs, Schottenbauer et al. (2008) found that non-response rates ranged from 20%-67% for PE, 3.6%-48% for CPT, and 7.3%-92% for EMDR. In a smaller but more recent review of treatment for combat-related PTSD, Steenkamp et al. (2015) found that 60%-72% of patients still met diagnostic criteria for PTSD after receiving CPT or PE. Response rates may be even lower in routine clinical practice; an analysis of 2,493 patient records from the English National Health Service (NHS) *Talking Therapies* programme found that only 32% of patients accessing trauma-focussed cognitive behavioural therapy (Tf-CBT) achieved reliable and clinically significant improvement in symptoms (Robinson et al., 2020). A contributing factor to nonresponse is poor acceptability of the psychological therapy and associated dropout. Lewis et al. (2020) systematically reviewed dropout from RCTs of psychological therapies for PTSD and found that the pooled dropout rate was 16% (95% CI [14, 18%]), suggesting that around one in six patients dropout.

Furthermore, dropout rates were higher for trauma-focussed therapies. The pooled dropout rate for EMDR was 18% (95% CI [12, 24%]), for PE was 22% (95% CI [16%, 28%]), and for CPT was 30% (95% CI [22%, 39%]). This highlights a dilemma, which is that patients with PTSD appear most likely to drop out from the treatments that are the most efficacious. As with treatment response, dropout rates may be even higher in routine clinical practice than in RCTs (Najavits, 2015).

One way that PTSD treatment outcomes might be improved is through personalised mental healthcare. This entails identifying the optimal treatment approach, length, or intensity, based on patients' individual characteristics (Cohen et al., 2021). There is evidence for heterogeneity in response to psychological therapy for PTSD (Herzog & Kaiser, 2022), and studies have found that patients with specific demographic and clinical characteristics may be more likely to respond to a specific trauma-focussed therapy (Deisenhofer et al., 2018; Keefe et al., 2018). For example, Deisenhofer et al. (2018) developed a statistical algorithm to identify patients who were more likely to respond to Tf-CBT than EMDR, and vice versa, based on pre-treatment demographic and clinical data. Implementing a treatment selection algorithm such as this in clinical practice has the potential to improve treatment outcomes by allocating individual patients to the treatment that is most likely to benefit them. Further, PTSD is a complex and heterogeneous condition (Galatzer-Levy & Bryant, 2013), and a number of studies have found evidence for subtypes of PTSD. For example, a "threat reactivity" subtype, high in intrusions, hyperarousal and avoidance, and a "dysphoric" subtype, high in anhedonia and negative affect (Campbell et al., 2020; Campbell-Sills et al., 2022; Horn et al., 2016; Pietrzak et al., 2014). Recent studies have found that patients with certain subtypes of depression respond differentially to CBT (Catarino et al., 2022; Simmonds-Buckley et al., 2021), and it is possible that this is also the case for PTSD (Forbes et al., 2003).

In psychotherapy outcome research, a large number of variables each explain a small proportion of variance in treatment outcome (Barawi et al., 2020; Dewar et al., 2020; Malejko et al., 2017), and it is likely that many of these variables covary, interact, or are non-linear. To account for this, researchers have begun to utilize machine learning (ML) methods (Aafjes-van Doorn et al., 2021), which are particularly well suited to analyse data of this nature (Chekroud et al., 2021). For example, penalised regression methods such as elastic net (Zou & Hastie, 2005) can perform predictor selection by shrinking coefficients for variables with little predictive value or high multicollinearity. Decision tree methods such as random forest (Breiman, 2001) can also implicitly handle complex non-linear relationships and interactions by sequentially dividing the data at the most informative threshold on important predictor variables.

ML is a data-driven approach that uses algorithms to detect patterns in data, with the goal of making accurate predictions in new data (Delgadillo, 2021). In this way ML methods are distinct from classical statistical methods, which predominantly aim to test hypotheses, make inferences, and explain variance within a particular sample (Bi et al., 2019; Yarkoni & Westfall, 2017). When applied optimally, the ML approach follows a sequence of six steps referred to as the *ML pipeline* (Delgadillo & Atzil-Slonim, 2022). These are [1] sample size calculation, [2] data pre-processing, [3] hyperparameter selection, [4] training the model, [5] testing the model with internal cross-validation, and [6] external validation of the model in independent data. Neglecting or inadequately performing any of the first five steps leads to *overfitting* (i.e., capitalising on the idiosyncrasies of the training data to the detriment of generalisability). Without step six, the extent of overfitting is unknown. The strength of evidence provided by ML studies can be categorised into three levels of increasing robustness: In *level 1* evidence, model performance is only evaluated within the training dataset without internal-cross validation; In *level 2*, internal cross-validation is applied; In *level 3*, the model is externally validated by applying the predictors and parameters selected during internal cross-validation to predict outcomes in independent data (Delgadillo & Atzil-Slonim, 2022).

Thus far, much of the research applying ML methods to predict psychological therapy outcomes has focussed on the treatment of depression and anxiety, and relatively little has focussed on treatment for PTSD (Aafjes-van Doorn et al., 2021; Lee et al., 2018; Sajjadian et al., 2021; Vieira et al., 2022). Ramos-Lima et al. (2020) systematically reviewed the use of ML methods in PTSD research but focussed primarily on studies that sought to predict the presence or onset of PTSD and did not include any studies that sought to predict the outcome of CPG recommended psychological therapies. Vieira et al. (2022) systematically reviewed studies that applied ML methods to predict outcomes for CBT, but this review excluded studies that predicted continuous outcomes (e.g., Deisenhofer et al., 2018), excluded other trauma-focussed psychological therapies (e.g., PE, EMDR), and only included one study that sought to predict outcomes in adults with PTSD (Zhutovsky et al., 2019). Further, the above reviews noted frequent methodological issues such as inadequate sample size and validation methods. If ML methods are not applied robustly then prediction models will not generalise and will be of little clinical utility. None of the previous reviews used a quality benchmark of the stages of a ML study provided by the *ML pipeline*.

Therefore, the present study aimed to conduct the first systematic review of studies that used ML methods to predict psychological therapy outcomes for PTSD. For the reasons outlined above, the focus of this review is on the application and reporting of each study's methods, benchmarked against the ML pipeline. The review question was framed following the recommendations of Moons et al. (2014) and Palazón-Bru et al. (2020) for framing systematic reviews of prognostic modelling studies and was reported following PRISMA guidelines (Page et al., 2021). After assessing risk of bias, study methods and results were synthesised, and the adherence to each step of the ML pipeline was evaluated.

2. Method

2.1. Pre-registration

The systematic review protocol was pre-registered with the PROSPERO database prior to conducting searches (Reference: CRD42022325021). The pre-registration can be accessed here: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022325021

2.2. Eligibility Criteria

Inclusion and exclusion criteria are described in Table 1. To be included any study must have applied ML methods to pretreatment data to predict the outcome of a psychological therapy recommended by clinical practice guidelines (CPG) as a first line treatment for PTSD in adults. CPG are intended to bridge the gap between evidence and practice by recommending treatments based on systematic reviews of empirical evidence and/or consensus in expert opinion (Hamblen et al., 2019). The inclusion criteria for this systematic review were guided by CPGs grounded in well conducted systematic reviews, which had been appraised to meet an acceptable quality standard using a standardised measure (Martin et al., 2021), and were published in the previous 5-years to ensure that they were contemporaneous (Shekelle et al., 2001). This included the following CPGs: American Psychological Association (2017), International Society for Traumatic Stress Studies (2018), National Institute for Health and Care Excellence (2018), Phoenix Australia Centre for Posttraumatic Mental Health (2021), and Veterans Affairs/Department of Defence (2017). The psychological therapies recommended in these CPGs (see Supplementary Table 1) were predominantly trauma-focussed cognitive behavioural therapies, exposure-based therapies, and EMDR.

2.3. Information Sources, Searching, and Screening

Pre-defined search terms were used to search four databases: APA PsycInfo (via Ovid), PTSDpubs (via ProQuest), PubMed, and Scopus. The search terms were designed to return any studies that mentioned any form of psychological therapy, PTSD or trauma, and any form of machine learning in the title, abstract or key words. The full search strategy is presented in Supplementary Materials. No limits, restrictions, or filters were applied. Databases were searched on 27th April 2022. The following review articles were checked for potentially eligible studies: Aafjes van-Doorn et al. (2021), Chekroud et al. (2021), Chen et al. (2022), Dewar et al. (2020), Dwyer et al. (2018), Hahn et al. (2017), Glaz et al. (2021), Malgaroli and Schultebraucks (2021), Manchia et al. (2020), Meehan et al. (2022), Ramos-Lima et al. (2020). Forward and backward citation searches for all eligible studies were performed using the R package *citationchaser* (Haddaway, 2021). The authors of all eligible studies were contacted to request further studies. Article metadata and abstracts for all search results were imported into EndNote 20 (https://endnote.com/). Duplicates automatically identified by EndNote 20 were screened and removed manually. Further duplicates were identified manually and removed during title and abstract screening. All titles and abstracts were manually screened against the inclusion and exclusion criteria in EndNote 20 by the first author, and full text files of potentially eligible studies were retrieved and screened.

2.4. Data Extraction and Synthesis

Relevant data from all eligible studies was extracted by the first author using a standardised data extraction table in Microsoft Excel, based on the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS; Moons et al., 2014), and the ML pipeline domains described by Delgadillo and Atzil-Slonim (2022). This included sample characteristics; treatment details; measures (including outcome and candidate predictor variables); ML methods and their purpose (e.g., predictor selection, prediction, clustering); pre-processing details; hyperparameter setting methods, validation methods, model evaluation metrics including accuracy (e.g., R^2, balanced accuracy), error (e.g., root mean squared error, mean absolute error), calibration, and discrimination (e.g., sensitivity, specificity, area under the receiver operating characteristic curve); predictors included in final model; relevant findings; and authors' interpretation of findings. When necessary, study authors were contacted via email to clarify methods and results. Study characteristics, methods, and findings were tabulated and summarised using a narrative synthesis. The pre-registered intention was to quantitatively synthesize prediction model performance metrics using random effects meta-analysis, but this was not possible due to heterogeneity of study methods. Studies adherence to the ML pipeline and corresponding level of evidence (apparent validation, internal cross-validation, external validation) was evaluated.

2.5. Risk of Bias Assessments

Risk of bias was assessed using the Prediction model study Risk Of Bias Assessment Tool (PROBAST; Moons et al., 2019). A second researcher independently conducted risk of bias assessments for 50% of the included studies. Cohen's kappa was calculated as a measure of agreement, discrepancies were discussed, and a third researcher was consulted where necessary. After consulting with a third researcher a unanimous decision was reached on all ratings.

3. Results

3.1. Study Selection

The study selection process is presented in the PRISMA diagram (see Figure 1). In total, 1,570 titles and abstracts were screened, 48 potentially eligible full texts were screened, and 17 studies met the inclusion criteria for the review. Full texts that were screened and excluded are presented in Supplementary Table 2 with reasons for exclusion. Frequent reasons for exclusion included: No ML methods used (*k* = 15), did not predict treatment outcome (*k* = 6), no CPG recommended therapy for PTSD (*k* = 6).

3.2. Study Characteristics

Study characteristics are presented in Table 2. Most studies conducted a retrospective analysis of data (*k* = 12), either from clinical trials (*k* = 5), cohort studies (*k* = 1), or routine clinical practice (*k* = 6). Five studies prospectively collected data for analysis, either as a clinical trial (*k* = 1) or cohort study (*k* = 4). Five studies sampled any adults seeking treatment for PTSD; six sampled from military populations; five specified PTSD related to interpersonal-, childhood-, or sexual-abuse; and two sampled patients with co-occurring mental health problems (substance use disorder and depression, respectively). Three studies included only female participants, and one study included only male participants. Participants received a range of CPG recommended psychotherapies for PTSD, most frequently PE (*k* = 10 studies), CPT (*k* = 6 studies), EMDR (*k* = 4 studies), or Tf-CBT (*k* = 3). Total sample size ranged from *N* = 57-612. All but one of the studies were published between 2018 and 2022. Nine studies were conducted in the USA, three in Germany, three in the Netherlands, one in Australia, and one was an analysis of data from England by a team of researchers in Germany and the UK.

3.3. Risk of Bias Assessments with PROBAST

Detailed risk of bias assessments are presented in Supplementary Table 3. The first and second rater initially agreed on seven out of nine studies, corresponding to a Cohen's kappa = 0.4, indicating *fair* agreement. Following consultation with a third researcher consensus was reached on all nine studies. All seventeen studies were rated at high risk of bias overall, primarily as all studies were high risk of bias in the *Analysis* domain. None of the studies had a reasonable number of participants with the outcome, and for some studies the number of predictor parameters estimated was unclear (studies often reported the number of candidate variables but did not report dummy coding of categorical variables or whether psychometric measures were entered as total scores, factors, or items). Although nine studies reported metrics of prediction accuracy, error, and/or discrimination, none of the studies reported calibration and therefore relevant model performance metrics were not evaluated appropriately. Thirteen studies did not include all enrolled participants in the analysis. Three studies inappropriately handled missing data and six studies did not provide information on the handling of missing data. Seven studies were rated at risk of bias due to selection of participants for using routinely collected clinical data or retrospective cohort study data.

3.4. Study Methods and Results

Study methods are presented in Table 3 and results are presented in Supplementary Table 4.

3.4.1 Outcome variable

Fourteen studies sought to predict treatment response but operationalised response in a variety of different ways. Eight studies sought to predict treatment response as a continuous outcome, five of which predicted change in PTSD score, two predicted post-treatment PTSD score, and one predicted post-treatment depression score as a proxy outcome (Deisenhofer et al., 2018). Six studies sought to predict treatment response as a categorical outcome, two of which predicted percentage change in PTSD score (50% and 30% respectively) as a binary outcome, one predicted reliable change in PTSD score as a binary outcome, two predicted latent trajectory class membership as a polytomous outcome (Hendriks et al., 2018; Nixon et al., 2021), and one predicted latent trajectory class membership as two binary outcomes (Held et al., 2022). The remaining three studies sought to predict treatment retention, two of which predicted a count of the number of sessions attended, and one predicted dropout as a binary outcome (Keefe et al., 2018).

3.4.2 Candidate Predictor Variables

Thirteen studies employed psychometric data (e.g., self-report or clinician-report measures of PTSD, depression, anxiety) as candidate predictor variables, eleven of these also used demographic data (e.g., gender, age, employment status), and eleven also used clinical data (e.g., diagnoses, medication use). Eleven studies tested baseline PTSD symptoms and PTSD-related cognitions as candidate predictors, and seven of these also tested trauma characteristics such as type of trauma and time since trauma. Four studies explored the relationship between neuroimaging data (MRI and EEG) and PTSD treatment outcomes. Number of candidate predictor variables ranged from approximately 5 to 104. Studies that used neuroimaging data did not specify the number of candidate predictors. See Supplementary Table 4 for details of candidate predictor variables.

3.4.3 Predictors Included in the Final Model

Among the fourteen studies sought to predict treatment response, all but one (Nixon et al., 2021) reported at least one significant pre-treatment predictor. Five studies included PTSD severity as a predictor in the final model, three of these also included trauma related variables; six studies included co-occurring mental health problems such as depression (*k* = 5) and emotion regulation difficulties (*k* = 2); and five included demographic variables such as age (*k* = 3) and gender (*k* = 3). Three studies using MRI data identified regions of the brain associated with treatment response, but there was no consensus (Etkin et al., 2019; Zhutovsky et al., 2019; Zilcha-Mano et al., 2020). Studies found that PTSD, trauma, and mental health related variables were stronger predictors of treatment response than demographic variables (Held et al., 2022; Herzog et al., 2021; Hoeboer et al., 2021; Stirman et al., 2021; Stuke et al., 2021). Three studies sought to predict treatment retention or dropout but there was no consensus among the predictors selected in the final model (Fleming et al., 2018; Keefe et al., 2018; López-Castro et al., 2021).

3.4.4. Machine Learning Methods

Studies used a range of different ML methods for various purposes. Fourteen studies used supervised ML methods. Eight studies used decision tree-based methods, and all but two of these used ensemble tree methods such as random forest and boosting algorithms (ADAboost, gradient boosted models). Three studies used a penalized regression method called *elastic net* (Held et al., 2022; Herzog et al., 2021; Stirman et al., 2021). Three studies used kernel methods (support vector machine, Gaussian process classifier) to analyse MRI data (Etkin et al., 2019; Zhutovsky et al., 2019; Zilcha-Mano et al., 2020). Five studies used unsupervised clustering (*k*-means) or dimension reduction methods (principal component analysis, independent component analysis). None of the studies used Bayesian ML methods or neural networks.

Five studies used the same ML method to perform feature selection, parameter estimation, and outcome prediction (Fleming et al., 2018; Held et al., 2022; Herzog et al., 2021; Kratzer et al., 2019; Nixon et al., 2021). Two studies used an unsupervised ML method for feature reduction and then used a supervised ML method for prediction (Stuke et al., 2021; Zhutovsky et al., 2019). Five studies used supervised ML methods to select predictors, and then used simpler statistical methods (e.g., linear regression, correlation) to test the relationship between the selected predictors and outcome (Hoeboer et al., 2021; Keefe et al., 2018; López-Castro et al., 2021; Stirman et al., 2021; Zilcha-Mano et al., 2020). One study used a genetic algorithm to select predictors for a linear regression model (Deisenhofer et al., 2018). One study used generalized linear modelling to select predictors and then used a supervised ML method to predict outcomes (Etkin et al., 2019).

Three studies used *k*-means cluster analysis: Zhang et al. (2021) used k-means to identify PTSD subtypes and then linear mixed models to test the relationship between subtypes and treatment outcome. Hendriks et al. (2018) used k-means to identify treatment response trajectory classes, and then used stepwise logistic regression to select predictors and predict trajectory class membership. Forbes et al. (2003) used *k*-means to test the reliability of PTSD subtypes identified by Ward's hierarchical cluster analysis, and then used generalized linear modelling to test differences in treatment response between subtypes.

Two studies compared the performance of more than one ML method (Etkin et al., 2019; Held et al., 2022), and two studies compared the performance of ML methods against that of traditional statistical methods (Held et al., 2022; Stuke et al., 2021).

3.4.5. Adherence to the ML Pipeline

The number of studies that reported each section of the ML pipeline is presented in Figure 2.

3.4.5.1. Sample Size Calculation

None of the studies reported a sample size calculation. The number of participants with the outcome in a model development sample ranged from < 36 (Etkin et al., 2019) to 397 (Herzog et al., 2021).

3.4.5.2. Data pre-processing

Nine studies reported handling of missing data, six of which reported multiple imputation. Three studies performed multiple imputation via random forest, but only one reported out-of-bag error estimates (Stirman et al., 2021). One study reported listwise exclusion of participants with missing data (Held et al., 2022); one excluded participants missing follow-up data (Zhutovsky et al., 2019); one excluded participants missing a whole scale and imputed mean values where <20% of a scale was missing (Stuke et al., 2021). Three studies reported reduction of categorical variables, one reported transformation of variables, one reported handling of class imbalance, and one reported case-control matching. Three of four studies that used neuroimaging data reported preprocessing of neuroimaging data. Four studies did not report any pre-processing of data.

3.4.5.3. Hyperparameter selection

Six studies reported using internal-cross validation to optimise hyperparameter settings, one of which also reported using default settings for some hyperparameters. Two studies only reported using default hyperparameter settings (López-Castro et al., 2021; Nixon et al., 2021). Two studies reported using statistical criteria (goodness of fit, gap statistic) to decide the number of k-means clusters (Hendriks et al., 2018; Zhang et al., 2021). Some studies reported setting for some but not all hyperparameters, and seven studies did not report hyperparameter setting. Most studies did not report the hyperparameters tested during optimisation, and none reported the optimal hyperparameter settings selected for the final model.

3.4.5.4. Cross validation and level of evidence

Eleven studies performed internal cross-validation: four performed *k*-fold, four performed leave-one-out, and two performed bootstrapping. One study also performed external validation in a randomly partitioned hold-out dataset (Herzog et al., 2021). As such, ten studies provided level 2 evidence and one study provided level 3 evidence.

Six studies did not perform internal cross-validation or external validation and therefore provided level 1 evidence. One of these studies (López-Castro et al., 2021) used the predictors selected in one dataset to make predictions in a second dataset, but repeated parameter estimation (model fitting) in the second dataset, and therefore performed replication rather than external validation. Another study (Zhang et al., 2021) divided the dataset into two cohorts and repeated *k*-

means clustering and linear mixed modelling in the second cohort, again performing replication rather than external validation.

3.4.6. Evaluation metrics

Nine studies reported metrics of model prediction accuracy or error. These studies all applied internal cross-validation procedures, but it is important to note that only Herzog et al. (2021) performed external validation, and none had a reasonable number of participants with the outcome. Therefore, model performance metrics were estimated within a training sample of insufficient size, limiting the likelihood that they will generalize to independent samples. None of the studies that sought to predict treatment retention reported evaluation metrics. None of the studies reported calibration.

Among the eight studies that sought to predict a continuous outcome, three reported model prediction accuracy in the form of R^2 or R, and four reported prediction error in the form of root mean squared error (RMSE), mean absolute error (MAE), and true error. Two of these studies reported both accuracy and error, and four studies did not report either. Herzog et al. (2021) used elastic net and reported R^2 = 0.17 (MAE = 0.69, RMSE = 0.91) in the training set (with bootstrap internal-cross validation) and R^2 = 0.16 (MAE = 0.77, RMSE = 0.95) in the hold-out external validation. Stirman et al. (2021) used elastic net to select predictors and reported R^2 = 0.39 (RMSE = 20.28) for prediction with linear regression mean averaged over 1000 repetitions of 10-fold internal cross-validation. Stuke et al. (2021) used principal component analysis to select predictors and reported R = 0.162 for prediction with ADAboost regressor and R = 0.214 for linear regression (when squared, ADAboost R^2 = 0.03 and linear regression R^2 = 0.05). Hoeboer et al. (2021) reported RMSE ranging from 4.06 to 7.24 when predicting change on two PTSD measures in two treatment groups (RMSE is referred to as *average error* in the publication and was clarified through correspondence with the author). Deisenhofer et al. (2018) reported *true error* (MAE of factual predictions) of 4.92 in one treatment group and 5.37 in the other.

Among the six studies that sought to predict a categorical outcome, two reported accuracy as raw accuracy or balanced accuracy, and three reported discrimination as area under the receiver operating characteristic curve (AUC-ROC), area under the precision-recall curve (AUC-PR), and/or sensitivity and specificity. Nixon et al. (2021) visually examined AUC-ROC but did not report statistics, and a further two studies did not report evaluation metrics for prediction of categorical outcomes. Held et al. (2022) tested six methods of developing a classification model and found that gradient boosted models produced the best predictions of fast response (AUC-PR = 0.466, AUC-ROC = 0.765) and elastic net produced the best predictions of minimal response (AUC-PR = 0.628, AUC-ROC = 0.826). Zhutovsky et al. (2019) used Gaussian process classifier to predict ≥ 30% reduction in PTSD score from MRI data and reported AUC-ROC = 0.929, balanced accuracy = 81.4%, sensitivity = 84.8%, specificity = 78%. Etkin et al. (2019) predicted ≥50% reduction in PTSD score from verbal memory delayed recall impairment and low within Ventral Attention Network connectivity (MRI) and reported accuracy = 85%, sensitivity = 80%, and specificity = 87% for linear SVM, and accuracy = 90%, sensitivity = 80%, and specificity = 93% for radial basis function SVM, but the sample size was particularly small (*n* = 36), the number of participants with the outcome was not reported, and class imbalance was not addressed.

3.4.7. Predicting Differential Treatment Outcome

Five studies explored interactions between pre-treatment variables and treatment type. Three studies sought to retrospectively predict the optimal treatment for each participant by developing a personalized advantage index (Deisenhofer et al., 2018; Hoeboer et al., 2021; Keefe et al., 2018). Following a method suggested by Kessler et al. (2017), Deisenhofer et al. (2018) and Hoeboer et al. (2021) used ML methods to select predictors for a linear regression model for each treatment under investigation and identified each patients' optimal treatment by comparing the outcomes predicted by the two regression models. Both studies found a significantly greater improvement in symptoms among patients who had received their model indicated optimal treatment. Keefe et al. (2018) used ML methods to select predictors and moderators (i.e., variables that interact with treatment type) for a logistic regression model and found a significantly lower rate of dropout among patients who received their model-indicated optimal treatment.

Stirman et al. (2021) sought to identify patients most likely to benefit from the most efficacious of two treatments, and those for whom treatment type was unlikely to make a difference, by developing a prognostic index (composite predictor) and testing its interaction with treatment type. The interaction explained 39% of the variance in post-treatment PTSD severity. All four of the above studies reported that using ML methods in this way could potentially guide personalized treatment selection for PTSD.

Zhang et al. (2021) investigated whether patients with latent subtypes of PTSD identified via *k*-means of EEG data, and not identifiable through clinical measures or demographic data, responded differentially to two treatments. There was a significant difference in post-treatment severity between the two subtypes, but no interaction with treatment type. Patients in this study were not randomly allocated to treatment and this was not addressed, therefore there is potential confounding by indication (Kyriacou & Lewis, 2016).

4. Discussion

This review aimed to identify and synthesize studies that used ML methods to predict the outcome of psychological therapy for PTSD, and the degree to which these studies adhered to best practice via auditing the methods of the studies against the ML pipeline domains. Through searching four databases and eleven similar systematic reviews, conducting forward and backward citation searches, and contacting the authors of eligible papers, seventeen studies were identified that met the inclusion criteria. Sixteen were published within the previous four years, reflecting a recent surge of interest in ML methods in clinical psychology and psychiatry (Aafjes-van Doorn et al., 2021), driven partly by recent advances in technology and data collection (Jordan & Mitchell, 2015), and the potential applications of ML methods to psychological therapy data (Chekroud et al., 2021). The one exception was published almost 20 years earlier, but this study made no reference to ML and simply used *k*-means to test the reliability of clusters identified via a different clustering method (Forbes et al., 2003).

4.1. Considerations Regarding Risk of Bias

Risk of bias assessments using PROBAST found all studies to be at high risk of bias. Specifically, all studies were rated high risk of bias in the *analysis* domain, primarily due to inadequate sample sizes for model training. Six studies were rated high risk of bias in the *participants* domain for using routinely collected practice data. Moons et al. (2019) suggest that routinely collected data is at higher risk of bias than RCT or prospectively collected data, as equivalent quality controls may not have been implemented. However, archival clinical practice data such as that of NHS Talking Therapies services is an available source of outcome data on a scale seldom seen in psychological therapy research, with treatments implemented with a high degree of standard training and supervision, and this may allow researchers to conveniently address the issue of sample size. More recently, mental health researchers have advocated the use of large electronic health records to optimise clinical prediction models, in view of the sample size limitations of typical clinical trials and the challenges related to data harmonization across clinical trial datasets, which often leads to sparse predictors (Delgadillo & Lutz, 2020; Kessler & Luedtke, 2021). Further, if the aim is to develop a prediction model for use in a particular mental health service, then using data from that same context may boost ecological validity and generalisability. Vieira et al. (2022) comment that using larger, more heterogeneous, naturalistic datasets may produce models with lower prediction accuracy but greater generalisability. Conversely, the finding that trauma related variables may be better predictors of outcome than demographic data presents a problem as many mental health services do not routinely collect this sort of data.

It is important to highlight that PROBAST was not developed to assess ML studies. Some argue that PROBAST may assess ML studies too harshly (Meehan et al., 2022), and others caution that ML methods may be at greater risk of bias under some conditions (Moons et al., 2019; van der Ploeg et al., 2014). Some important features of ML are not assessed by PROBAST, such as hyperparameter selection, which was not reported by seven out of the seventeen studies in this review and can lead to overfitting if performed inappropriately (Delgadillo & Atzil-Slonim, 2022). The inconsistent reporting and application of ML methods identified by this review reiterates the call for specific guidelines and risk of bias assessment tools (Meehan et al., 2022; Vieira et al., 2022), which were under development at the time when this review was conducted (Collins et al., 2021).

4.2. Sample Size

The finding that none of the studies reported a sample size calculation is congruent with similar reviews of clinical prediction modelling with ML methods (Aafjes-van Doorn et al., 2021; Balki et al., 2019). Determining an appropriate sample size for a developing a clinical prediction model using ML methods is a complex task that depends on several factors. Riley et al. (2020) recently published guidelines for estimating the required sample size that go beyond EPV and other rules of thumb. However, the appropriate sample size also varies according to the particular ML method, with some methods requiring larger samples to develop stable models (Dalmaijer et al., 2022; Giesemann et al., 2023; Riley et al., 2021; van der Ploeg et al., 2014), and according to the internal cross-validation methods applied. In a simulation study, Vabalas et al. (2019) found that *k*-fold internal cross-validation yielded over-optimistic estimates of accuracy compared to nested *k*-fold and randomly partitioned hold-out validation, and the magnitude of the bias had an inverse relationship with sample size, increasing sharply with sample size $N < 100$. Additionally, Vabalas et al. (2019) found that the bias increased with the number of candidate predictor variables. A commonly applied rule of thumb is that a minimum of ten outcome events per variable (EPV) is required to train a prediction model. However, this is contentious as it is not empirically-based, and Moons et al. (2019) suggest that an EPV of 20 may be more robust. More precisely it is the number of variable parameters in the model that is of interest (i.e., dummy coded categories and interactions between variables each require the estimation of additional parameters), and when the outcome is categorical the number of outcome events refers to the number of participants in the smallest category. Studies in this review did not consistently explicitly report the number of candidate predictor variables tested, and where they did it was unclear whether they were reporting the number of variables or number of parameters.

Notably, the four studies that used neuroimaging data did not report the number of candidate predictor parameters. Analysing neuroimaging data typically requires estimation of many parameters, and therefore a large number of participants with the outcome. However, Zhutovsky et al. (2019) and Etkin et al. (2019) had the two smallest samples, and Etkin et al., (2019) did not report the number of participants with the outcome. All four of these studies identified regions of the brain significantly associated with PTSD treatment response, but with little consensus, and none were externally validated. Etkin et al. (2019) and Zhutovsky et al. (2019) reported accuracies > 80% but this was likely due to overfitting. Similarly, Vieira et al. (2022) found that studies that used neuroimaging data to predict CBT outcomes reported higher accuracy but again had smaller sample sizes, suggesting that the higher estimates of accuracy were due to overfitting. Collecting neuroimaging data is more expensive, time-consuming, and imposes a higher degree of patient burden than collecting questionnaire or patient health record data. This makes the acquisition of an appropriate sample size to analyse high dimensional neuroimaging data even more challenging. Further, this raises doubts about the feasibility of implementing clinical prediction models that require this type of data at scale, particularly in large publicly funded health services.

4.3. External Validation

The finding that only one study (Herzog et al., 2021) employed external validation procedures is congruent with recent reviews of prediction modelling in clinical psychology (Aafjes-van Doorn, 2021; Chekroud et al., 2021; Meehan et al., 2022; Vieira et al., 2022). Moreover, this study only externally validated the model in a randomly split hold-out sample. Some argue that this is not an optimal form of external validation, as the training set and validation set are subsamples of the same dataset, are likely to be highly correlated, and provide overestimates of model performance (Aafjes-van Doorn et al., 2021; Steyerberg, 2019). Splitting the data by time (temporal validation) or geographic location (geographic validation) is a more stringent test of external validity (Steyerberg, 2019). Further, some studies had the opportunity to externally validate a model in an independent sample but replicated model fitting and reported the statistical significance of predictors instead of evaluating model performance metrics (López-Castro et al., 2021; Zhang et al., 2021). This suggests a reluctance amongst researchers to shift from testing hypotheses and seeking to explain relationships between variables, to developing pragmatic prediction models (Yarkoni & Westfall, 2017). As such, the extent to which any of the prediction models reviewed here would generalise beyond the respective training sample is unclear. Further, the generalisability of a prediction model is limited by the make-up of the training sample, and a number of studies in this review included only male or only female participants, potentially limiting the generalisability of the model.

4.4. Evaluating Model Performance

Eight studies did not report model performance evaluation metrics, including two that applied internal cross-validation (Keefe et al., 2018; Nixon et al., 2021), and none of the studies examined calibration. Therefore, it is unclear how efficacious and reliable these models are at predicting therapy outcomes for patients with PTSD. Only two studies compared the performance of ML methods to traditional statistical methods: Held et al. (2022) found that five different ML models outperformed logistic regression, but Stuke et al. (2021) found that ordinary linear regression performed slightly better than ADABoost (an ensemble decision tree method). Therefore, it is unclear whether ML methods offer an advantage over traditional statistical methods, particularly as neither of these studies tested prediction models in an independent validation sample. In a systematic comparison of ML methods and logistic regression, Christodoulou et al. (2019) found that

ML methods were more accurate than logistic regression, but only when high risk of bias studies were included in the comparison, suggesting that any apparent advantage of ML methods over logistic regression are a product of study bias. However, this review included penalised logistic regressions in the non-ML logistic regression category, and some would consider these ML methods (Bi et al., 2019; Delgadillo & Atzil-Slonim, 2022; Webb et al., 2020). Further research is required to investigate whether the complexity added by ML methods improves clinical prediction accuracy to a meaningful degree and index the true extent of this advantage. Additionally, some ML methods may be better than others at predicting treatment outcomes, but only two studies compared the performance of more than one ML method (Etkin et al., 2019; Held et al., 2022).

Four studies applied supervised ML methods to develop a prediction model, but then entered the predictors into a simpler statistical model to estimate parameters and predict outcomes, thereby forgoing any potential advantages of the ML model. López-Castro et al., (2021) commented that variables selected by random forest were not all significant predictors in Poisson regression and suggest that this may be due to correlation with other variables (multicollinearity). However, Poisson regression also makes assumptions about the distribution of the data and the shape of the relationship between the predictor and outcome variables that random forest does not (Mushagalusa et al., 2022).

4.5. Predictors in Final Models

The finding that pre-treatment levels of PTSD, depression, and other mental health problems were among the most consistently selected predictors in a final model is congruent with previous systematic reviews and meta-analyses of predictors of PTSD treatment outcome, which found that these variables were associated with worse outcomes (Barawi et al., 2020; Dewar et al., 2020; Kline et al., 2021; Olatunji et al., 2010). Similarly, the finding that clinical variables were more important predictors than demographic variables is congruent with systematic reviews that found inconsistent support for demographic variables as predictors of PTSD treatment outcome (Barawi et al., 2020; Haagen et al., 2015).

4.6. Recommendations for Future Studies

To achieve the potential for ML methods to improve individual prediction of psychological therapy outcomes for PTSD, it is recommended that future studies demonstrate full adherence to the ML pipeline domains described above. Specifically, this can achieved in the following ways: [1] perform a sample size calculation and acquire a suitably powered dataset; [2] perform multiple imputation of missing data (stratified by treatment group; Zhang et al., 2021) and report data pre-processing in detail; [3] report all hyperparameter setting (using automated grid search or values selected *a priori*); [4] apply internal cross-validation during model development and testing; [5] externally validate (don't repeat model fitting) in a temporally and/or geographically independent samples (Steyerberg, 2019), and evaluate and report accuracy, error, discrimination, and calibration. Additionally, it is recommended that studies compare the performance of multiple ML methods against one another and against the simplest comparable method (e.g., linear regression or logistic regression).

If ML methods are applied in samples that are too small, with no internal cross-validation, and manual hyperparameter tuning, then it is likely that the model will be overfitted to the training data and estimates of model performance will be over-optimistic. Without external validation and calibration, the extent of the optimism and whether the model will generalise is unknown. A recent meta-analysis of ML models found a negative association between study quality and estimates of prediction accuracy, suggesting that poorer quality studies overestimate accuracy (Sajjadian et al., 2021). It is worth noting that for a prediction model to be clinically useful, the model's prediction accuracy does not necessarily need to be high, only better than expert clinical judgement (Ægisdóttir et al., 2006; Cearns et al., 2019). This can be tested in a prospective randomised trial once the external validity of a prediction model has been established (e.g., Delgadillo et al., 2022). The recently published TRIPOD+AI statement (Collins et al., 2024) guides transparent reporting of clinical prediction models, including those that used ML. This may also serve as an additional guide when designing studies.

4.7. Limitations

ML is an umbrella term that encompasses a broad range of methods, and studies do not always use the term "machine learning". Efforts were made to perform as wide a search as possible; nonetheless it is possible that some relevant studies were not found. Further, the distinction between ML and traditional methods is not clearly defined, and it is possible that some methods included in this review would not be considered ML by some, and vice versa (Bi et al., 2019). In line with the pre-registration, only studies published in peer reviewed journals were included. This is common practice in psychological therapy reviews, aids replicability of the search procedures, and reduces the likelihood of inclusion of poor-quality studies (Aafjes-van Doorn et al., 2021). However, some relevant studies may have been excluded for this reason (e.g., Cohen, 2018). This review focussed specifically on the prediction of outcome from pre-treatment or baseline data, in the interest of applying ML methods to predict the optimal treatment for individual patients. However, there are other ways that the application of ML methods could potentially improve PTSD treatment outcomes, for example by providing personalised outcome feedback and recommendations during treatment (Bone et al., 2021; Lutz et al., 2019). EndNote 20 reference management software was used to organise and screen search results, and citationchaser (Haddaway, 2021) used to conduct forward and backward citation searches. However, use of AI assisted systematic review tools, such as Rayyan (https://www.rayyan.ai/) and Covidence (https://www.covidence.org/), may have increased efficiency and accuracy of searching and screening.

4.8. Clinical Implications

This systematic review highlights the need for services to critically evaluate clinical prediction models developed using ML before adopting and applying the recommendations into routine practice. In particular, services should consider the sample size, the level of evidence (indicated by the presence of internal and/or external cross-validation procedures), and assessments of calibration and discrimination (Delgadillo & Atzil-Slonim, 2022; Steyerberg, 2019).

4.9. Conclusion

Due to the methodological limitations and omissions of the studies identified by this systematic review, it is unclear whether ML methods offer any advantages over traditional statistical methods at predicting psychotherapy outcomes for PTSD. Studies neglected to recruit a sample of an appropriate size informed by a sample size calculation, report hyperparameter setting, perform internal and external cross-validation, and assess model calibration. Whilst ML methods may have the potential to improve the prediction of treatment outcomes for PTSD, in order to achieve this potential, ML methods need to be applied rigorously and be shown to offer an added benefit over traditional prediction methods.

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Declaration of interest

None.

Figure 1 *PRISMA Flow Diagram*

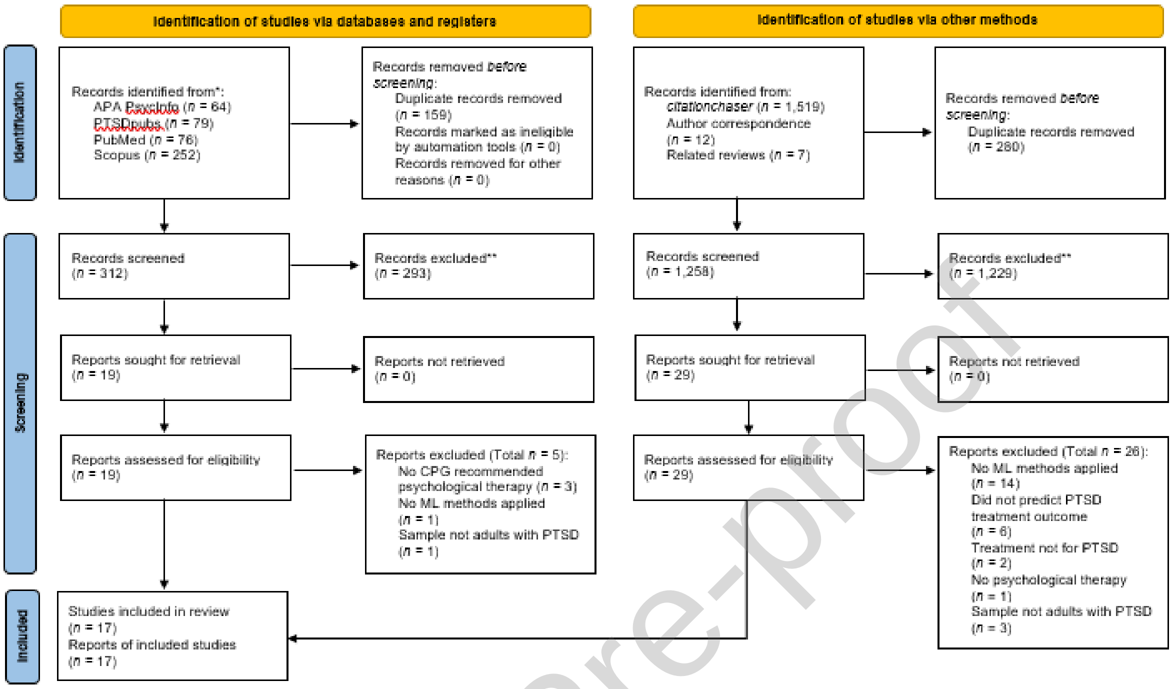
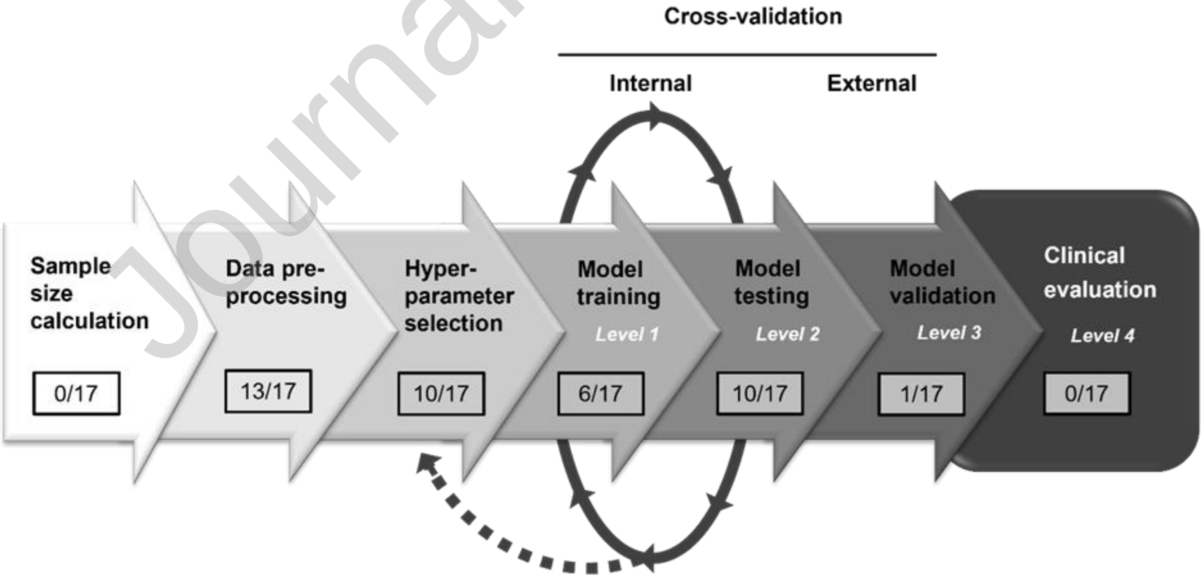

Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from*:
APA PsycInfo (n = 64)
PTSDpubs (n = 79)
PubMed (n = 76)
Scopus (n = 252)
Records removed before screening:
Duplicate records removed (n = 159)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Records identified from:
citationchaser (n = 1,519)
Author correspondence (n = 12)
Related reviews (n = 7)
Records removed before screening:
Duplicate records removed (n = 280)
Records screened (n = 312)
Records excluded** (n = 293)
Records screened (n = 1,258)
Records excluded** (n = 1,229)
Reports sought for retrieval (n = 19)
Reports not retrieved (n = 0)
Reports sought for retrieval (n = 29)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 19)
Reports excluded (Total n = 5):
No CPG recommended psychological therapy (n = 3)
No ML methods applied (n = 1)
Sample not adults with PTSD (n = 1)
Reports assessed for eligibility (n = 29)
Reports excluded (Total n = 26):
No ML methods applied (n = 14)
Did not predict PTSD treatment outcome (n = 6)
Treatment not for PTSD (n = 2)
No psychological therapy (n = 1)
Sample not adults with PTSD (n = 3)
Studies included in review (n = 17)
Reports of included studies (n = 17)

Figure 2 *Proportion of Studies Reporting Each Step of the Machine Learning Pipeline*



Note. Figure adapted from Delgadillo and Atzil-Slonim (2022)

Table 1 *Inclusion and Exclusion Criteria*

	Inclusion Criteria	Exclusion Criteria
Population	Adults (aged 18 and over) who received clinical practice guideline recommended psychological therapy for current PTSD.	Children and adolescents under the age of 18. Adults receiving treatment for a condition other than PTSD.
Intervention	Evidence-based psychological therapies recommended for the treatment of current symptoms of PTSD in adults by current clinical practice guidelines.	Psychological therapy intended to treat a different condition. Psychological therapy intended to prevent the onset or relapse of PTSD. Pharmacological therapy. Non-psychological therapy (e.g., acupuncture or yoga). Psychological therapy not recommended by clinical practice guidelines. (If any of the above were delivered alongside or in comparison to an intervention that met the inclusion criteria then that study would be included.)
Outcome to be predicted	Continuous or categorical outcomes of psychotherapy for PTSD, including	Future onset or relapse of PTSD. Current presence (diagnosis) of PTSD.

	remission, change in symptoms, dropout, and retention.	
Time span of prediction	From pre-treatment to post-treatment. The outcome timepoint of interest is the end of treatment, or the follow-up nearest to the end of treatment.	
Intended moment of model use	Initial patient assessment, prior to the start of treatment.	During or after treatment.
Modelling approach	Prognostic models that applied supervised or unsupervised machine learning methods in the prediction of treatment outcomes from patients' pre-treatment or baseline features.	Diagnostic models that predict the presence of PTSD. Prognostic models that predict onset of PTSD. Modelling approaches that did not use any machine-learning methods.
Scope/intended purpose of models	To guide clinical decision-making and treatment planning.	

Note. PTSD = Post-Traumatic Stress Disorder.

Table 2 *Study Characteristics*

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
Deisenhofer et al. (2018)	Routine clinical practice (Retrospective)	Adults with PTSD (317)	NHS primary care outpatient mental health service (England)	Tf-CBT (242) EMDR (75)	≤ 20 weekly sessions (Session duration not reported)
Etkin et al. (2019)	RCT (Prospective)	Adults with PTSD (76)	University (U.S.A.)	PE (36) Wait-list control (30)	9 or 12 weekly or twice-weekly 90-minute sessions
Fleming et al. (2018)	Routine clinical practice (Retrospective)	Military veterans with PTSD (124)	Veterans Affairs speciality outpatient clinic (U.S.A.)	PE (49) CPT (53) Opted out of psychological therapy following introductory psychoeducation session (22)	Mean (SD) *n* sessions attended = 6.78 (7.03) (Session duration not reported)
Forbes et al. (2003)	Routine clinical practice (Retrospective)	Military veterans with PTSD (166)	Veterans PTSD treatment programme (Australia)	Group and individual therapy, primarily cognitive-behavioural in orientation, with trauma-focussed sessions (166)	16 sessions of individual therapy over 12 weeks (4 weeks inpatient, 8 weeks outpatient)

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
					(Session duration not reported)
Held et al. (2022)	Cohort study (Prospective)	Military veterans with PTSD (502)	University Medical Centre Intensive Outpatient Treatment Program (U.S.A.)	CPT based intensive PTSD treatment program (502)	14 once-daily 50-minute sessions of individual CPT over 3 weeks
Hendriks et al. (2018)	Cohort study (Prospective)	Adults with PTSD and history of multiple interpersonal traumas (73)	Outpatient mental health clinic (Netherlands)	Intensive PE (73)	12 sessions over 4 days within 1 week (4.5 hours per-day), followed by 4 weekly 90-minute booster sessions with homework
Herzog et al. (2021)	Routine clinical practice (Retrospective)	Adults with PTSD (612)	Five specialized inpatient clinics (Germany)	Individual exposure therapy (PE, IRRT, or EMDR), plus group Tf-CBT and a range of supplementary psychological	8 to 10 weeks, 1 hour per week individual exposure therapy, 8 hours per week of group Tf-CBT, plus an

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
				and non-psychological therapies (612)	average of 11 hours per week of multimodal and transdiagnostic interventions (total 152-200 therapy hours) Sample mean (SD, range) length of stay (days) = 54.3 (15.5, 6 - 98)
Hoeboer et al. (2021)	RCT (Retrospective; Oprel et al., 2021)	Adults with childhood-abuse-related PTSD (149)	Two specialist outpatient mental health services (Netherlands)	PE (48) Intensified PE (51) STAIR+PE (50)	PE: 16 weekly 90-minute sessions Intensified PE: Three PE sessions per-week for 4 weeks, followed by booster PE sessions after 1 month and 2 months (total 14 sessions)

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
					STAIR+PE: Eight sessions of STAIR followed by eight sessions of PE
Keefe et al. (2018)	RCT (Retrospective; Resick et al., 2002)	Women with rape-trauma PTSD (160)	(U.S.A.)	CPT (79) PE (81)	Total 13 hours for each treatment over 6 weeks CPT: 12 sessions of 50-60 minutes, with 30 minutes added to each of the two writing exposure sessions (sessions 4 and 5) PE: Nine sessions; one 60-minute initial session followed by eight 90-minute sessions

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
Kratzer et al. (2019)	Routine clinical practice (Retrospective)	Inpatients with complex PTSD following childhood physical and childhood sexual abuse (150)	Specialist inpatient clinic (Germany)	Tf-CBT, often with integrated exposure and EMDR. Patients also offered group psychotherapies . (150)	≤ 20 individual psychotherapy sessions of 75-minutes each

López-Castro et al. (2021)	RCT (Retrospective; Ruglass et al., 2017; Hien et al., 2015)	Adults with PTSD and SUD (130)	Community based outpatient mental-health treatment programme (U.S.A.)	Sample 1 (Ruglass et al., 2017):
				1. COPE (33)
				2. RPT (37)
				
				Sample 2 (Hien et al., 2015):
				1. Seeking Safety plus placebo (29)
				2. Seeking Safety plus ADM (31)
					Sample 1 (Ruglass et al., 2017):
					All participants were offered 12 weekly 90-min individual sessions
					
					Sample 2 (Hien et al., 2015):
					All participants were offered 12 weekly 60-min individual psychotherapy sessions, and ADM (sertraline) dosage started on 50 mg/day

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
					and increased up to 200 mg/day over 2 weeks throughout the active study period
Nixon et al. (2021)	RCT (Retrospective; Galovski et al., 2012, Galovski, Harik, Blain, Elwood, et al., 2016; Resick et al., 2002, 2008)	Female interpersonal trauma survivors (216)	Community (U.S.A.)	CPT (216)	12 weekly or bi-weekly 60-min sessions
Stirman et al. (2021)	RCT (Retrospective; Schnurr et al., 2007)	Female military veterans and active-duty service members with PTSD (267)	Nine VA medical centres, two VA readjustment counselling centres, and a military hospital (U.S.A.)	PE (135) Present-Centred Therapy (132)	10 weekly 90-minute sessions
Stuke et al. (2021)	Routine clinical practice (Retrospective)	Adults with PTSD (209)	Specialist day clinic (Germany)	CBT based day-care programme including individual CPT (209)	Four sessions per-week of individual CPT, plus group trauma-

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
					focussed therapy 5 days per-week, for a mean of 8.59 weeks (SD = 1.4) (Session duration not reported)
Zhang et al. (2021)	Cohort study (Prospective); non-randomised clinical trial (Prospective)	Military veterans with PTSD (241); trauma-exposed controls (95)	University; Veterans Affairs PSTD clinic (U.S.A.)	PE or CPT (135)	Based on manualised protocols (Foa et al., 1999; Resick, 2001) (Number of sessions and session duration not reported)
Zhutovsky et al. (2019)	Cohort study (Prospective)	Male military veterans with PTSD (57); combat-exposed controls (29)	Four military mental-healthcare outpatient clinics (Netherlands)	Tf-CBT (8) EMDR (28) Tf-CBT+EMDR (8)	Mean (SD) number of treatment sessions: Responders = 9.86 (6.29) Non-responders = 10.05 (4.22) (Session duration not reported)

Study	Data Source	Population (Total Sample *N*)	Setting (Country)	Treatment (Group *n*)	Treatment Duration
Zilcha-Mano et al. (2020)	Cohort study (Retrospective)	Adults with PTSD (51); adults with PTSD and depression (52); trauma-exposed controls (76)	State Psychiatric Institute (U.S.A.)	PE (55)	10-week standard PE protocol (Session duration not reported)

Note. ADM = Anti-Depressant Medication; CBT = Cognitive Behavioural Therapy; COPE = Concurrent Treatment for Substance Use Disorder and Post-Traumatic Stress Disorder Combining Prolonged Exposure and Relapse Prevention Therapy; CPT = Cognitive Processing Therapy; EMDR = Eye Movement Desensitization And Reprocessing; IRRT = Imagery Rescripting and Reprocessing Therapy; NHS = National Health Service; PE = Prolonged Exposure; PTSD = Post-Traumatic Stress Disorder; RCT = Randomized Control Trial; RPT = Relapse Prevention Therapy (treatment for substance use disorder); Seeking Safety = skills-based intervention for concurrent post-traumatic stress disorder and substance use disorder; STAIR = Skills Training in Affective and Interpersonal Regulation; SUD = Substance Use Disorder; Tf-CBT = Trauma-focussed Cognitive Behavioural Therapy; VA = Veterans Affairs.

Table 3 *Study Methods*

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
Deisenhofer et al. (2018)	Post-treatment symptom severity (continuous, PHQ-9 as a proxy measure of PTSD) Optimal treatment for each patient	Final treatment session	Clinical, demographic, psychometric (11)	Genetic algorithm (predictor selection, *n* = 150; 75)	Linear regression (parameter estimation, calculate PAI, *n* = 150; 75) Chi-squared test (compare rate of reliable improvement between patients who received model indicated optimal vs. suboptimal treatment, *n* = 225)	NR	Multiple imputation via random forest (on whole sample) Categorical predictors reduced to dichotomous variables (employment, medication) Propensity score matching	Importance threshold set at 80% Other hyperparameter settings not reported	Leave-one-out cross-validation	2
Etkin et al. (2019)	≥50% reduction in PTSD score	4 weeks after final treatm	MRI, EEG, neurocognitive tests (unclear)	Linear support vector machine; Non-linear	Generalized linear modelling (neurocognitive predictor	NR	Threshold in delayed recall score indicative of	NR	Leave-one-out cross-validation	2

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
	(binary, CAPS)	ent session		radial basis function support vector machine (predict treatment outcome, *n* = 36, outcome frequency not reported)	selection, *n* = 92 including *n* = 36 controls; neuroimaging predictor selection, *n* = 87 including *n* = 36 healthy controls) Generalized linear mixed modelling (test interactions with treatment, *n* = 36, vs. control, *n* = 30)		impaired recall identified by discriminant analysis (*n* = 92) Preprocessing of neuroimaging data described in supplementary materials			
Fleming et al. (2018)	Retention (count, *n* sessions completed)	Final treatment session	Clinical, demographic, psychometric, military service characteristics,	Exhaustive CHAID classification tree (predictor selection, parameter		NR	NR	NR	NR	1

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
			trauma characteristics (51)	estimation, prediction, *n* = 122)						
Forbes et al. (2003)	Change in symptom score (continuous, PCL)	3 months post-treatment; 9 months post-treatment (*n* = 136)	Psychometric (16)	k-means cluster analysis (test reliability of subgroups identified by Ward's cluster analysis, *n* = 158)	Ward's hierarchical cluster analysis (identify subgroups of PTSD patients, *n* =158) Second order principal components analysis (reduce MMPI-2 scale and aid interpretation of results, *n* = 158) Multivariate generalized linear modelling (explore	NR	NR	NR	NR	1

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
					differences in outcome and independent variables between clusters, *n* = 158) Repeated measures multivariate generalized linear modelling (examine differences in treatment response between subgroups, *n* = 158)					
Held et al. (2022)	Minimal response (binary, PCL-5); Fast response (binary, PCL-5)	Intake, treatment days 2, 3, 5, 6, 8, 11, and 13, and post-	Demographic, psychometric, military service characteristics, trauma	Elastic Net classification; Gradient Boosted Models; Random Forest;	Group-based trajectory modelling (identify response trajectory class)	NR	Listwise exclusion of participants with missing data	Hyperparameter optimisation via five-fold cross-validated grid search within inner loop	Five-fold cross-validation	2

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
		treatment	characteristics (104)	Ridge classification; Logistic Regression with Max-Min Parent-Child variable selection (predictor selection, parameter estimation, prediction, *n* = 432 including *n* = 73 with minimal response outcome and *n* = 61 with fast response outcome)	Logistic Regression (comparison with ML methods)		One-hot-encoding of categorical variables Performance assessed by area under the precision-recall curve to account for class imbalance	of nested five-fold cross validation Hyperparameter tuning not required for logistic regression or logistic regression with max-min parent-child variable selection Hyperparameter settings not reported		
Hendriks et al. (2018)	Response trajectory class	Baseline, 3 month follow	Clinical, demographic,	k-means cluster analysis (identify	Stepwise multinominal logistic regression	NR	Multiple imputation of missing	Varied number of clusters from 3 to 6	NR	1

Study	**Outcome(s) to be predicted (variable type, measure)**	**Outcome Time-Point**	**Predictor type (number of candidate predictor variables)**	**Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)**	**Additional methods (purpose, *n* participants analysed)**	**Sample size calculation**	**Data pre-processing**	**Hyperparameter setting**	**Validation methods**	**Evidence level**
	(polytomous, CAPS)	up, 6 month follow up	psychometric (14)	response trajectory class, *n* = 69)	(predictor selection and prediction, *n* = 69)		data following a framework for multiple imputation in cluster analysis Participants missing baseline CAPS score were excluded (*n* = 4)	and evaluated goodness of fit Other hyperparameter settings not reported		
Herzog et al. (2021)	Change in symptom score (continuous, IES-R)	First and last day of treatment	Clinical, demographic, psychometric (≥ 46)	Elastic net (predictor selection, parameter estimation, prediction, *n* = 397)		NR	Participants missing > 60% and variables missing > 40% were excluded Univariate outlier values removed Time-event	L1 and L2 penalty weighting alpha set to 0.5 Optimal lambda value estimated by *k*-fold cross-validation averaged across 10 runs	Bootstrap internal cross-validation in training set (*n* = 397) External validation in randomly partitioned (35%) hold-out	3

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
							data log-transformed Categorical variables were reduced to binary or continuous variables (details not reported), ICD-10 medical diagnoses were dummy coded Binary variables with class imbalance were excluded Multiple imputation via random	(within training set) Optimal lambda value not reported	validation set (*n* = 215)	

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
							forest (separately on training and test set)			
Hoeboer et al. (2021)	Change in symptom score (continuous, CAPS-5; PCL-5) Optimal treatment for each patient	4 weeks, 8 weeks, and 16 weeks after start of treatment	Clinical, demographic, psychometric (24)	Boruta algorithm random forest classifier (predictor selection, *n* = 99; 50)	Linear mixed-effect modelling (estimate change in symptoms over the course of treatment for each participant, *n* = 149) Linear regression (parameter estimation, prediction, *n* = 99; 50)	NR	NR	NR	Bootstrapping (predictor selection) Leave-one-out cross-validation internal cross-validation (prediction, PAI)	2
Keefe et al. (2018)	Dropout (binary, treatment completion)	Final treatment session	Clinical, demographic, psychometric, trauma	Bootstrapped, random forest variant of model-based	Logistic regression (parameter estimation,	NR	Participants who dropped out prior to randomisation	NR	Five-fold cross-validation	2

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
	Optimal treatment for each patient		characteristics (20)	recursive partitioning (MoB), and bootstrapped variant of an AIC-based backward selection model (predictor selection, *n* = 160 including *n* = 49 with dropout outcome)	prediction, *n* = 160)		excluded from analyses (*n* = 11) Single-dataset random forest imputation strategy using all available pre-treatment and outcome data			
Kratzer et al. (2019)	Reliable change (binary, IES-R)	Before discharge	Clinical, psychometric (5)	Conditional inference tree (predictor selection and prediction, *n* = 150 including *n* = 78		NR	Bayesian multiple imputation	NR	NR	1

Study	**Outcome(s) to be predicted (variable type, measure)**	**Outcome Time-Point**	**Predictor type (number of candidate predictor variables)**	**Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)**	**Additional methods (purpose, *n* participants analysed)**	**Sample size calculation**	**Data pre-processing**	**Hyperparameter setting**	**Validation methods**	**Evidence level**
				with reliable change outcome)						
López-Castro et al. (2021)	Treatment attendance (count, *n* sessions attended)	Final treatment session	Clinical, demographic, psychometric, trauma characteristics (28)	Iterative Random Forest (predictor selection, *n* = 70)	Poisson regression (parameter estimation, prediction, *n* = 70; 60)	NR	NR	Default hyperparameter settings used, values not reported	Parameter estimation repeated in independent dataset (training set *n* = 70; replication set *n* = 60)	1
Nixon et al. (2021)	Response trajectory class (polytomous, PDS/PSS)	Post-treatment, follow up 3 to 9 months after final session	Clinical, demographic, psychometric, trauma characteristics (38)	Random forests of conditional inference trees (predictor selection and prediction, *n* = 179)		NR	Classified response trajectories identified based on symptom scores at session 1, session 6, posttreatment and follow-up	Default hyperparameter settings used, values not reported	Internal validation as part of random forest (bagging)	2

Study	**Outcome(s) to be predicted (variable type, measure)**	**Outcome Time-Point**	**Predictor type (number of candidate predictor variables)**	**Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)**	**Additional methods (purpose, *n* participants analysed)**	**Sample size calculation**	**Data pre-processing**	**Hyperparameter setting**	**Validation methods**	**Evidence level**
Stirman et al. (2021)	Post-treatment symptom severity (continuous, CAPS)	Post-treatment	Clinical, demographic, psychometric, trauma characteristics (29)	Elastic net, five iterations, predictors retained if selected on all five iterations. Then stepwise AIC-penalized bootstrapped variable selection with 10,000 bootstrapped samples, predictors retained if selected in >60% samples (predictor selection, *n* = 267)	Linear regression with 10-fold cross-validation, coefficients mean averaged across 1000 runs (parameter estimation, generate PI, *n* = 267) Linear regression (test association between PI and outcome, and interaction between PI and treatment type, *n* = 267)	NR	Binary variables effect-coded Continuous predictors standardised Multiple imputation via random forest (OOB error estimates reported)	Elastic net alpha parameter set to .75, lambda optimized via 10-fold cross-validation Optimal lambda not reported	10-fold cross-validation	2

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
Stuke et al. (2021)	Change in symptom score (continuous, DTS)	Discharge	Clinical, demographic, psychometric, trauma characteristics (12)	Principal component analysis (predictor reduction, *n* = 115) ADAboost regressor (parameter estimation, prediction, *n* = 115)	Linear regression (comparison with ADAboost regressor, *n* = 115)	NR	Participants missing responses to a whole scale excluded; scale mean imputed where participants were missing <20% responses to scale (*n* = 10)	Optimal number of components for each participant estimated via hyperparameter optimisation with 10-fold cross-validation in (*N* - 1) training set, varying number of components from 1-10 and comparing squared error ADAboost: *n* estimators optimized with 10-fold cross-validation in training set (candidates: 2, 5, 10,	Leave-one-out cross-validation	2

Study	**Outcome(s) to be predicted (variable type, measure)**	**Outcome Time-Point**	**Predictor type (number of candidate predictor variables)**	**Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)**	**Additional methods (purpose, *n* participants analysed)**	**Sample size calculation**	**Data pre-processing**	**Hyperparameter setting**	**Validation methods**	**Evidence level**
								20, 40); default settings used for other hyperparameters Hyperparameter settings not reported		
Zhang et al. (2021)	Post-treatment symptom severity (continuous, CAPS; CAPS-5)	NR for PTSD data	EEG/PEC (unclear)	Sparse k-means clustering (identify PTSD subtypes, *n* = 106)	Linear mixed models (predict outcome from subtype, *n* = 72; *n* = 63)	NR	Multiple imputation reported for depression dataset but not for PTSD dataset EEG and MRI preprocessing reported in methods section	Number of clusters (2) determined and assessed by the gap statistic Sparsity parameter optimised by inner-loop cross-validation, value not reported	k-means repeated on 100 randomly selected subsamples (random 90% of the sample in each subsample) PTSD treatment outcomes dataset divided into two	1

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
									cohorts, cluster analysis applied, and linear mixed modelling repeated in the second cohort	
Zhutovsky et al. (2019)	≥30% reduction in PTSD score (binary, CAPS)	6 to 8 months from baseline assessment	MRI (unclear)	Independent component analysis using the meta-ICA approach (dimension reduction, *n* = 28 controls) Gaussian process classifier (predictor selection and predictio	Univariate analysis with threshold-free cluster enhancement and permutation analysis (dimension reduction, *n* = 44)	NR	Participants missing follow-up data were excluded from analysis, and 3 participants were excluded due to excessive movement during MRI MRI pre-processing reported in	NR	10-fold cross-validation	2

Study	Outcome(s) to be predicted (variable type, measure)	Outcome Time-Point	Predictor type (number of candidate predictor variables)	Machine learning methods (purpose, *n* participants analysed, *n* with categorical outcome)	Additional methods (purpose, *n* participants analysed)	Sample size calculation	Data pre-processing	Hyperparameter setting	Validation methods	Evidence level
				n, *n* = 44 including *n* = 20 with treatment response outcome)			supplementary material			
Zilcha-Mano et al. (2020)	Change in symptom score (continuous, CAPS)	Pre to post-treatment	MRI (unclear)	Linear kernel support vector machine with *t*-test filtering and wrapper based sequential predictor selection (predictor reduction and selection, *n* = 179)	Pearson correlations (test correlation between predictors and treatment outcome, *n* = 55)	NR	Excluded 3 participants due to excessive movement during MRI Predictors regressed for age, sex, and MRI scanner, and normalized (-1 1) MRI preprocessing reported in supplementary materials	Hyperparameter optimisation (kernel scale and function) during 10-fold cross-validation, settings not reported	10-fold cross-validation during support vector machine training Correlations not cross-validated	1

Note. AIC = Akaike Information Criterion; CAPS = Clinician-Administered PTSD Scale; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CHAID = Chi-square Automatic Interaction Detection; DTS = Davidson Trauma Scale; EEG = Electroencephalography; ICD-10 = International Classification of Diseases 10th Revision; IES-R = Impact-of-Event-Scale-Revised; MMPI-2 = Minnesota Multiphasic Personality Inventory-2; MRI = Magnetic Resonance Imaging; NR = Not Reported; OOB = Out-Of-Bag; PAI = Personalised Advantage Index; PCL = PTSD Checklist; PCL-5 = PTSD Checklist for DSM-5; PDS = Posttraumatic Stress Diagnostic Scale; PEC = Power Envelope Connectivity; PHQ-9 = Patient Health Questionnaire-9; PI = Prognostic Index; PSS = Post-traumatic Symptoms Scale; PTSD = Post-traumatic Stress Syndrome; RCT = Randomised Controlled Trial.

Declaration of Competing Interest

The authors declare that they have no known potential competing interests that could affect the objectivity of the work presented in this paper.

Highlights

- All were rated high risk of bias, primarily due to inappropriate sample size.
- None of the studies reported every step of the machine learning pipeline.
- Just one reported external validation, in randomly partitioned hold-out sample.
- Two studies compared machine learning to traditional methods, with mixed results.
- ML may advance precision treatment for PTSD but methods must be applied rigorously.