Published in final edited form as:

JAMA. 2018 August 28; 320(8): 825–833. doi:10.1001/jama.2018.10574.

Will this adult patient develop severe alcohol withdrawal? The Rational Clinical Examination Systematic Review

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Abstract

Importance: Although severe alcohol withdrawal syndrome (SAWS) is associated with substantial morbidity and mortality, most at-risk patients will not develop this syndrome. Predicting its occurrence is important because the mortality rate is high when untreated.

Objective: To assess the accuracy and predictive value of symptoms and signs for identifying hospitalized patients at risk of SAWS, defined as delirium tremens, withdrawal seizure, or clinically diagnosed severe withdrawal.

Data Sources: MEDLINE and EMBASE (1946-January 2018) were searched for articles investigating symptoms and signs predictive of SAWS in adults. Reference lists of retrieved articles were also searched.

Study Selection: Original studies that were included compared symptoms, signs, and risk assessment tools among patients who developed SAWS and patients who did not.

Data Extraction and Synthesis: Data were extracted and used to calculate likelihood ratios (LRs), sensitivity, and specificity. A meta-analysis was performed to calculate summary LR.

Results: Of 530 identified studies, 14 high-quality studies that included 71295 patients and 1355 relevant cases of SAWS (1051 cases), seizure (53 cases), or delirium tremens (251 cases) were analyzed. A history of delirium tremens (LR, 2.9 [95% CI 1.7–5.2]) and baseline systolic blood pressure 140 mm Hg or higher (LR, 1.7 [95% CI, 1.3–2.3]) were associated with an increased likelihood of SAWS. No single symptom or sign was associated with exclusion of SAWS. Six high-quality studies evaluated combinations of clinical findings and were useful for identifying patients in acute care facilities at high risk of developing SAWS. Of these combinations, the

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Financial Disclosures: None declared for EW, LA, ST, CG, KA, SN, MM, JK.

Online-only material: eTables and eFigure available at www.jama.com

Prediction of Alcohol Withdrawal Severity Scale (PAWSS) was most useful, with an LR of 174 (95% CI, 43–696; specificity, 0.93) when patients had 4 or more individual findings and an LR of 0.07 (95% CI, 0.02–0.26; sensitivity, 0.99) when there were 3 or fewer findings.

Conclusions and Relevance: Assessment tools that use a combination of symptoms and signs are useful for identifying patients at risk of developing severe alcohol withdrawal syndrome. Most studies of these tools were not fully validated, limiting their generalizability.

CLINICAL SCENARIO

Case:

A 67-year-old woman was admitted to the emergency department for a minor head laceration that occurred after a fall resulting from alcohol intoxication. She was alert, oriented, looked well and had a pulse of 120 beats per minute. Her blood alcohol level was 210 mg/dL (45.6 mmol/L). She said for the past 5 years she drank 8 beers per day and has previously been admitted to residential addiction treatment programs but has never seen an addiction medicine physician. For some, but not all, of her prior attempts at alcohol cessation, she became mildly tremulous. She did not have a history of blackouts, withdrawal seizures, delirium tremens or other substance use, including benzodiazepines. Eight hours after her last drink, she looked well, was no longer intoxicated, and her heart rate was unchanged at 120 beats per minute. She was otherwise stable and asked about outpatient addiction treatment. Despite her well appearance, her physicians were concerned about the potential risk for developing delirium tremens or alcohol withdrawal seizures when she would be discharged to home and stop drinking alcohol. Can risk factors, symptoms, or signs be used to predict the probability of severe alcohol withdrawal?

WHY THIS QUESTION IS IMPORTANT

Globally, harmful use of alcohol is responsible for approximately 33 deaths per 100,000 people annually and approximately 85 million disability-adjusted life-years.¹ The prevalence of at-risk or heavy alcohol use tends to be higher among adults actively seeking healthcare than estimated prevalence rates in the general population.^{2–4}

One serious consequence of chronic alcohol use is the potential for severe alcohol withdrawal when its use is reduced or stopped. Severe alcohol withdrawal syndrome is characterized by intense autonomic and psychological symptoms, withdrawal seizures and/or delirium tremens. Severe alcohol withdrawal can contribute to substantial morbidity such as aspiration pneumonia, arrhythmia, and myocardial infarction,⁵ and historically was associated with a mortality rate as high as 15%.^{6,7} With more aggressive prevention and management, alcohol withdrawal is now associated with lower mortality rates on the order of 3%.⁸ The National Institute on Alcohol Abuse and Alcoholism and the American Psychiatric Association have developed standardized criteria for at-risk drinking and alcohol withdrawal syndrome respectively (see Box 1).^{9,10}

To prevent severe alcohol withdrawal, various pharmacotherapeutic and programmatic strategies such as inpatient withdrawal management have been developed. Appropriate identification, prophylaxis and treatment of withdrawal is essential to reduce morbidity and

mortality associated with this disorder. Because there is a high prevalence of at-risk or heavy alcohol use, yet severe alcohol withdrawal is relatively uncommon and its treatment is costly and risky, there is a need to accurately identify patients having a high risk for developing severe alcohol withdrawal.

PHYSIOLOGIC BASIS FOR ALCOHOL WITHDRAWAL SYNDROME

The pathophysiology of alcohol withdrawal is incompletely understood. Alcohol is believed to primarily affect the central nervous system (CNS) by facilitating the actions of *gamma*-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Alcohol increases the inhibitory effects of the GABA_A receptor, while also suppressing the brain's major excitatory neurotransmitter, glutamate, at the *N*-methyl-D-aspartate (NMDA) receptor.⁵ Chronic, heavy alcohol use results in adaptive changes to the GABA and glutamate neurotransmitter systems to compensate for the effects of alcohol on neural pathways and to restore neurochemical equilibrium.¹¹ Sudden cessation of or a significant reduction in alcohol consumption triggers an acute neurotransmitter imbalance with rapid decline in inhibitory GABA activity and increased excitatory glutamate/NMDA activity, resulting in overall CNS hyperactivity and reduced threshold for seizures.¹¹

SYMPTOMS AND SIGNS PREDICTIVE FOR SAWS

Up to 50% of individuals with a history of long-term, heavy alcohol consumption will experience some degree of mild withdrawal when alcohol use is stopped.^{12–14} Symptoms usually appear during the first 24 hours of abstinence. Within hours of stopping alcohol use, autonomic hyperactivity can occur manifested by tachycardia, tremor, nausea, vomiting and sweating. These may be accompanied by psychological symptoms such as anxiety, restlessness, sleep disturbance or insomnia. Signs of alcohol withdrawal include diaphoresis, tremor, tachycardia, hypertension, hyperthermia, and disorientation. Transient visual, auditory and/or tactile hallucinations occur in about 2–8% of individuals.^{15,16} While alcohol withdrawal is usually limited to these symptoms, approximately 10% of symptomatic individuals experience withdrawal-related generalized tonic-clonic seizures,^{17,18} which require medical management. If left untreated, about 1/3 of patients having withdrawal seizures are at risk for progression to delirium tremens.¹⁹ Delirium tremens is the most serious manifestation of alcohol withdrawal. It is characterized by severe confusion, disorientation and/or hallucinations accompanied by severe autonomic hyperactivity.²⁰ Delirium tremens occurs in 3–5% of patients who are hospitalized for the management of alcohol withdrawal.^{21,22}

Universal screening of all patients in acute care environments for at-risk or heavy drinking identifies patients who are at increased risk of alcohol-related harms, including severe alcohol withdrawal (see Box 1 Definitions of at-risk drinking and alcohol withdrawal syndrome).^{23,24} Since patients may underreport amount and frequency of alcohol use, efforts to accurately quantify alcohol intake are important (see eBox 1 in the supplement; Approximate drinking equivalents). Family members may validate or refute patient reports, especially when the patient is unable to provide their own history. Patients meeting criteria for at-risk or heavy drinking should be asked about when they had their last drink. They

should also be asked about past alcohol cessation attempts resulting in alcohol withdrawal and what symptoms and signs were associated with the withdrawal. Given the high prevalence of polysubstance use, patients should be asked about the use of other substances. When assessing a patient for alcohol withdrawal, a blood alcohol level, complete blood count, electrolytes, and liver function tests should be obtained. The likelihood of progression to more severe symptoms, seizures, or delirium tremens should also be assessed in all patients with alcohol use disorders, even those who are not experiencing withdrawal, or who have mild symptoms of withdrawal.

This Rational Clinical Examination systematically reviewed the diagnostic accuracy of a range of clinical findings, symptoms and signs used to predict the risk of severe alcohol withdrawal symptoms, seizures, and delirium tremens.

METHODS

Search Strategy and Quality Review

Eligible studies were assessed that compared alcohol use history, symptoms of alcohol withdrawal, laboratory findings and physical examination findings between patients who did or did not subsequently develop severe alcohol withdrawal (eTable 1 in the supplement). To identify relevant articles, MEDLINE and EMBASE from 1946 to January 2018 were searched. The search strategy used terms including *withdrawal*, *alcohol drinking*, the MESH term *Substance Withdrawal Syndrome* and terms previously found to be useful for retrieving diagnostic studies (see eAppendix Search Strategy in the supplement).²⁵ Additional studies were identified by searching reference lists of original and review articles. Studies that evaluated past experiences with alcohol and past symptoms of alcohol withdrawal, and physical examination and laboratory findings were included. Studies were excluded if they only described clinical examination findings for patients with severe withdrawal. Review papers not reporting original data were also excluded.

Two authors (CG and ST/LA) independently reviewed abstracts for inclusion into this analysis and assessed study quality using the Levels of Evidence from the PRISMA-compliant Rational Clinical Examination handbook.²⁶ Using this schema, Level 1 indicated the highest quality and was assigned to studies that had independent blinded comparison of the symptoms or signs with a valid criterion standard in a large number of consecutive patients (greater than 150).²⁶ Level 2 studies were similar to level 1 studies but enrolled fewer than 150 patients. Level 3 studies enrolled nonconsecutive patients. Level 4 studies used non-independent comparisons among a “convenience” sample of patients at risk of having the condition in question. Sources of bias were also evaluated with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Tool (eTable 2 in the supplement).^{26–28}

Statistical Methods

The population incidence of severe alcohol withdrawal after alcohol cessation was estimated from reports of the US National Institute on Alcoholism and Alcohol Abuse and World Health Organization,^{13,29,30} The incidence of individual alcohol withdrawal symptoms was

estimated from the 14 studies included in this review. The summary incidence was calculated as a random effects estimate from the included studies.

To evaluate the sensitivity, specificity, and likelihood ratios (LR), 2×2 contingency tables were constructed for each symptom and sign. The reliability of symptoms and signs was quantified with the kappa (κ) statistic. Data were entered into Microsoft Excel spreadsheets predesigned to calculate the sensitivity, specificity, LRs, and their 95% CIs.³¹ To create summary measures and limit potential bias, only studies that met the standards of Level 1, 2, or 3 of the Rational Clinical Examination criteria were included.²⁶

Rating scales and measures used to define of severe alcohol withdrawal syndrome have traditionally involved a range of criteria (see Box 1), but the definition has not been consistent in the literature or over time.³² For the purpose of this review, we identified cases of severe alcohol withdrawal as determined by individual study authors (see eTable 1 in the supplement). While delirium tremens and seizures may occur as an initial presentation, we considered the manifestations of withdrawal along a continuum from mild to severe withdrawal symptoms that may also progress to seizures and delirium tremens. Therefore, if a study reported all 3 outcomes (severe alcohol withdrawal syndrome, delirium tremens, and seizures), to avoid double counting of events within patients, the study result was only considered as having the severe alcohol withdrawal syndrome outcome. Similarly, if a study reported severe alcohol withdrawal syndrome and delirium tremens, only severe alcohol withdrawal syndrome was counted. Finally, if a study reported both delirium tremens and seizure, only delirium tremens was counted.

When a symptom or sign was assessed in only one high quality study, the LR and 95% confidence interval (CI) were reported for dichotomous variables or the standardized mean difference (SMD) for continuous variables. When a symptom or sign was assessed in two studies, the range for the LR or SMD was reported.³³ When considered in three studies, LR data was pooled using separate univariate random-effects meta-analysis (*Comprehensive Metaanalysis* Version 2.0. Englewood, NJ: Biostat; 2005)³⁴ and the I^2 statistic was reported to supplement the information from the confidence interval about the dispersion of results.^{35,36}

Continuous variables were reported by calculating the standardized mean difference (SMD). SMDs reported the differences between patients who developed severe alcohol withdrawal syndrome from those who did not. The SMD is calculated by dividing the mean difference between groups by the standard deviation of the measurement.³⁷ SMDs are unitless, reporting information as multiples of the standard deviation, facilitating comparisons between groups irrespective of the measurement scale. The greater the absolute value of the SMD, the better the finding differentiates those who will be affected from those who will not. A general suggestion for interpreting the magnitude of the SMD is to recognize that the SMD is an effect size where values of approximately |0.2| represent small differences between groups, |0.5| represent moderate differences, and |0.8| or greater indicate potentially large recognizable differences.³⁸

RESULTS

Search Results

The systematic search identified 530 studies that were reviewed, with 50 articles eligible for qualitative synthesis (eFigure 1 in the supplement). These 50 studies all included patients with a reasonable index of suspicion of alcohol withdrawal risk, ranged in size from 19 – 36,331 patients and included research and clinical studies of individuals presenting to alcohol withdrawal management units and hospitals, including for medical reasons other than alcohol withdrawal (eTable 1 in the supplement). Of these 50 studies, 14 met the study quality criteria for Level 1 – 3 by the Rational Clinical Examination Quality Checklist with bias addressed adequately on most items of the QUADAS tool (eTables 1–3 in the supplement).^{27,28} Details of study site characteristics are reported in eTable 1. These 14 higher quality studies included a total of 71,295 patients and 1,355 relevant cases of severe alcohol withdrawal syndrome (1051 cases), seizure (53 cases) or delirium tremens (251 cases) (eTable 1 in the supplement).

Incidence of alcohol withdrawal syndrome:

The incidence of severe alcohol withdrawal syndrome is higher in studies designed to assess diagnostic accuracy of risk factors, symptoms and signs than in population-based surveys, which report that fewer than 1% of the general population experienced severe alcohol withdrawal symptoms in the year prior to being surveyed.³⁰ The incidence also depends on the patient population, care setting and reason for admission (e.g., inpatient withdrawal management vs. general hospital admission). Across three studies of patients admitted to withdrawal management facilities, the incidence of severe alcohol withdrawal syndrome was 23% (95% CI 20–27%, $I^2=0\%$).^{39–41} The incidence of alcohol withdrawal syndrome is much lower among at-risk patients admitted to general medical units. The incidence was 1.9% (95% CI 1.2–3.1%) for acute medical admissions where patients were identified by having a score greater than 8 on the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C),⁴² and the incidence was 6.7% (95% CI 4.6–9.6%) among acute medical admissions when patients had a positive blood alcohol concentration (BAC > 200 mg/dL) or a history of any drinking in the prior 30 days.²

The incidence of alcohol withdrawal syndrome among general hospitalized patients is low. In consecutive trauma patients, the incidence of severe alcohol withdrawal syndrome was 0.40% (95% CI 0.33–0.48%)⁸ and it was 0.67% (95% CI 0.58–0.75%) for alcohol withdrawal syndrome of any severity in general medical-surgical patients.⁴³ Among adults (with available BAC) admitted to a single, academic, tertiary Level I trauma center following motor vehicle accidents, 10% (95% CI 9.3–11%) of all patients developed an alcohol withdrawal syndrome.⁴⁴

Reliability of the Clinical Diagnosis of Severe Alcohol Withdrawal

In a survey of 173 patients recruited from inpatient and outpatient substance abuse treatment facilities in the U.S., the inter-rater reliability using the Diagnostic and Statistical Manual of Mental Disorders criteria for the diagnosis of alcohol withdrawal was excellent ($\kappa = 0.80$ [range 0.71 – 0.89]).⁴⁵ Maldonado *et al.* (2015) evaluated the inter-rater reliability in a

random sample of 49 patients and found moderate to substantial agreement in the diagnosis of alcohol withdrawal syndrome.² In a study of a random sample of 103 patients hospitalised with a diagnosis of alcohol withdrawal syndrome, inter-rater reliability between two blinded physicians for making the diagnosis was excellent ($\kappa = 0.75$ [95% CI, 0.66 – 0.84]).⁴³ In a survey of 400 randomly selected patients from eight regional facilities in the U.S., test-retest reliability of the diagnosis of alcohol withdrawal syndrome was good-excellent with Interclass Correlation Coefficient (ICC) = 0.82 [95% CI, 0.78–0.84].⁴⁶ Sullivan *et al.* (1989) showed an excellent interrater reliability when using the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) for the diagnosis of alcohol withdrawal syndrome among a random sample of 100 patients ($r > 0.8$).⁴⁷ When the same patient was evaluated twice by the same interviewer, test-retest reliability was also consistent.⁴⁸

Risk Factors, Symptoms and Signs

Risk Factors.—A history of delirium tremens was the most frequently studied finding (three articles) and increased the likelihood that a patient will subsequently develop severe alcohol withdrawal upon alcohol cessation (summary LR 2.9, 95% CI 1.7–5.2, see Table 1). Some patients will experience seizures during a current alcohol cessation attempt prior to presenting for medical care. Patients who have had 3 or more seizures (LR 2.8, 95% CI 1.4–5.9) or 1–2 seizures (LR 1.6, 95% CI 1.4–2.2) during their current alcohol cessation attempt have an increased risk of progressing to severe alcohol withdrawal syndrome. A history of withdrawal seizures (LR range 0.47–1.7) during prior alcohol cessation episodes appeared to be less useful in predicting risk of severe alcohol withdrawal syndrome than a history of delirium tremens.

Men were no more likely than women to have severe alcohol withdrawal syndrome, (summary LR for men 1.3, 95% CI 1.0–1.7). Caucasians were no more likely than non-Caucasians to have severe alcohol withdrawal syndrome (summary LR for Caucasians 1.1, 95% CI 1.0–1.2). Among continuous variables (Table 2), patients who developed severe alcohol withdrawal were younger than patients who did not, though the effect size was small (summary SMD –0.27, 95% CI –0.49 to –0.05; $p=0.016$).

Individual studies have reported that patients with a concurrent substance use disorder or mental health condition (e.g., mood disorder or anxiety disorder) have an increased risk of severe alcohol withdrawal (Table 1). Based on three studies, the absence of a history of delirium tremens had a small effect on identifying patients less likely to have severe alcohol withdrawal (LR 0.78, 95% CI 0.67–0.91). There were no risk factors with a likelihood ratio of smaller than 0.5 that would predict the likelihood of not developing severe alcohol withdrawal.

Symptoms and Signs.—No individual symptoms were reported in the studies that met our inclusion criteria. A systolic blood pressure ≥ 140 mmHg at admission was associated with increased likelihood of severe alcohol withdrawal (summary LR 1.7, 95% CI 1.3–2.3)

A normal systolic blood pressure was associated with identifying patients less likely to have severe alcohol withdrawal (LR 0.78, 95% CI 0.69–0.89). However, when evaluated as a

continuous measure, those who develop severe alcohol withdrawal cannot be distinguished by either the systolic blood pressure (range SMD -0.70 to 0.38) or the diastolic blood pressure (range SMD -0.47 to 0.32). While tachycardia is a hallmark of autonomic excitability, the heart rate had a very small effect size for identifying groups of patients more likely to have severe alcohol withdrawal (range SMD 0.01 to 0.06).

Laboratory findings.—One study suggested that blood alcohol concentration 200 mg/dL (LR 3.5 , 95% CI 3.0 – 4.0) was associated with increased likelihood of developing withdrawal, and that a blood urea nitrogen > 26 mg/dL obtained at hospital admission (LR 3.3 , 95% CI 1.4 – 7.6) was associated with increased likelihood of developing delirium tremens.⁴⁹ Another study suggested that thrombocytopenia ($<150 \times 10^3/\mu\text{L}$) was associated with an increased risk of delirium tremens (LR 2.2 , 95% CI, 1.4 – 3.4).⁵⁰

When evaluated as continuous variables (Table 2), two criteria have SMD effect sizes larger than 0.8 . Groups of patients with a higher serum gamma-glutamyl transferase (GGT; range SMD 0.03 to 1.4) or a higher serum aspartate aminotransferase (AST; range SMD 0.07 to 0.88) might have higher incidences of severe alcohol withdrawal. The effect size and narrow range of the SMD for serum alanine aminotransferase (ALT) approaches 0 (range SMD 0.04 to 0.18), which suggests that the ALT may be less useful than the AST. Lower levels of serum potassium (range SMD -0.73 to -0.20) or lower platelet counts (range SMD -0.59 to -0.35) were associated with identifying patients at risk for severe alcohol withdrawal symptoms.

Combinations of Symptoms and Signs

Because individual findings have relatively low LR+ and high LR-, and effect sizes for continuous variables do not clearly identify patients most likely to have or not have severe alcohol withdrawal, several different composite measures have been evaluated (see Table 1).

In six studies, nine different composite measures were used to identify patients at risk for developing severe alcohol withdrawal syndrome.^{2,8,39–41,51} None of the composite measures were validated after their initial report. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (Box 2), which was developed for medically ill inpatients, has the best LR+ and the best LR-.² The PAWSS requires recording the presence or absence of 9 different risk factors (recent alcohol intoxication, blood alcohol level $> 200\text{mg/dL}$, previous withdrawal, history of withdrawal seizures, history of delirium tremens, previous alcohol rehabilitation treatment, prior blackouts, use of benzodiazepines or barbiturates, other substances of misuse) and one sign (increased autonomic activity) as part of the scale (Box 2). Among the PAWSS validation sample, having 4 or more signs or risk factors made severe withdrawal much more likely (LR 174 , 95% CI 43 – 696), whereas having fewer than 4 signs or risk factors was associated with an LR of 0.07 (95% CI, 0.02 – 0.26). PAWSS sensitivity was 0.93 (95% CI 0.77 – 0.99) and specificity was 0.99 (95% CI 0.98 – 0.99). Considering the baseline incidence rate of approximately 5% among individuals hospitalized for alcohol withdrawal,²² if the PAWSS was validated in new populations, the positive predictive value (PAWSS ≥ 4) would be 93% and the negative predictive value (PAWSS < 4) would be 99%.

Prior research has investigated why these instruments seem to have such a high diagnostic test performance.⁵² For PAWSS, incorporation bias is likely because it includes increased autonomic activity in its score. One point on the 10 point PAWSS scale is given when any one of the following is present: HR > 120, tremor, sweating, agitation or nausea. Of the remaining 9 points, 8 are questions about patients' past experience. Because all of the questions are equally weighted, any signs of increased autonomic activity would not disproportionately increase the total PAWSS score, and would not necessarily be required to obtain a positive score. 4. Nonetheless, because increased autonomic activity is included in the criteria for diagnosing severe withdrawal, its inclusion in PAWSS likely accounts for its high sensitivity and specificity.

The Luebeck Alcohol Withdrawal Scale (LARS)³⁹ relies on a patient's clinical history, physical examination and laboratory testing (for a full list of scale items, see eTable 7 in the supplement). The LARS-10 total score is calculated from 10 findings, yielding a score ranging from 0–14. A score of 1 is added when each of the following are present: frequent sleep disturbance in the past week, nightmares during the last week, polyneuropathy, ataxia, or BAC ≥ 100mg/dl. When the BAC ≥ 100mg/dl, an additional point is added for each of the following if present: tremor, sweating, and pulse rate ≥ 100bpm. Three points are added when there is a history of 3 or more episodes of delirium tremens and for 3 or more episodes of withdrawal seizures (for a total of 6 if both are present). A score of 9 or more on LARS-10 is associated with a greater likelihood of severe withdrawal (LR 12, 95% CI 5.8–27), whereas having a score of less than 9 is associated with an LR of 0.05 (95% CI 0.02 – 0.37). The sensitivity of LARS-10 as a test for predicting severe alcohol withdrawal is 0.95 (95% CI 0.77–0.99) and specificity is 0.93 (95% CI 0.88–0.94). The items considered in a 20-item and an 11-item version of LARS are shown in eTable 7 in the supplement.

Limitations

This review has several limitations. First, although the original search yielded 50 original studies reporting information about risk factors for severe alcohol withdrawal, only 14 high quality articles were identified. These 14 articles included more than 70,000 patients and 1,300 cases of severe alcohol withdrawal syndrome, seizure or delirium tremens. One concern relevant to any observational study examining disease prognosis is the potential for biases related to study quality. Both the JAMA Rational Clinical Examination Criteria and the QUADAS tool to assess study quality were used in this review. This quality assessment resulted in the exclusion of 12 of the 17 studies used in an earlier meta-analysis on this topic.¹³ While some biases likely persist, some studies, including the development of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), involved a range of protections against bias including a separation between staff assessing study participant PAWSS scores and those diagnosing and treating severe alcohol withdrawal.

Second, the current evidence base was developed during an era when effective treatments for preventing severe alcohol withdrawal exist which affects the natural history of alcohol withdrawal.⁵³ While not appropriate for all circumstances (e.g., non-verbal patients),⁵⁴ the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) is often used to measure the severity of withdrawal symptoms (i.e., not predict risk of developing future withdrawal) and

used to guide administration of benzodiazepine prophylaxis to avoid worsening symptoms. The CIWA can reduce incidence of delirium tremens (−4.9 cases per 100 patients) and seizures (−7.7 seizures per 100 patients).⁵⁵ In the present review, CIWA use was reported in 7 of the 14 higher quality studies, while the remaining studies used other approaches (see QUADAS Tool, eTable 3 in the supplement).⁴⁷ There was too much variation in the CIWA threshold values used to establish a diagnosis of severe alcohol withdrawal to perform a meta-analysis (range: 8 to 15; see eTable 1 in the supplement). A baseline CIWA score appeared useful in a single study⁸ and was included among the “six independent correlates” that comprised a composite measure used in the study by Kraemer *et al.* (2003).⁴¹ Although CIWA and other tools affect the natural history of alcohol withdrawal, assessing the accuracy of signs and symptoms is best undertaken in the context of current best practices that include the use of these measures.

Third, the criterion standard for establishing a diagnosis was not consistent across studies assessed in this review (see eTable 1 in the supplement). Some studies only assessed components of severe withdrawal syndrome such as seizure rather than the entire syndrome itself. In this review, severe alcohol withdrawal syndrome was assessed rather than individual symptoms or signs that are associated with the syndrome.

SCENARIO RESOLUTION

Case:

This patient presented to the emergency department with known history of alcohol use disorder. Establishing a pretest probability for the incidence of severe alcohol withdrawal syndrome requires clinical judgment and awareness of the variability in outcome based on the setting and the planned treatment to lower the risk of withdrawal. Since she has a known alcohol use disorder and is being admitted to the hospital without prolonged sobriety, her risk for developing severe withdrawal in an acute care setting is approximately 5%²² or if she was admitted to a withdrawal management specialty hospital, it would be 20%.^{39–41} Using the results from Table 1, none of this patient’s individual symptoms or signs are particularly helpful for determining the likelihood of subsequent severe withdrawal with the exception of her blood alcohol level 200 mg/dL (LR 3.5, 95% CI 3.0–4.0, Table 1). However, her PAWSS score was 4 (based on her intoxication, alcohol treatment history, previous withdrawal symptoms and blood alcohol level. When her PAWSS score > 4 (LR 174, 95% CI 43–696, Table 1) is applied to the pre-test probability of 5%, increases her likelihood of developing severe alcohol withdrawal to approximately 90%. Regardless of the environment considered for assessing pre-test risk, based on the findings of this review, she requires continued admission, supportive care and a therapeutic strategy (e.g., benzodiazepine prophylaxis) to prevent the emergence of severe withdrawal.^{56,57}

CLINICAL BOTTOM LINE

Patients admitted to a general medical hospital who have a history of heavy alcohol use have an approximately 2–7% chance of developing severe alcohol withdrawal and if they are admitted to a specialized treatment center that likelihood is increased to approximately 20%. Few individual symptoms or signs predict withdrawal or effectively predict it will not occur.

Of the individual findings that can be obtained from a clinical examination, a history of delirium tremens is the most effective (summary LR 2.9, 95% CI 1.7–5.2) for identifying a risk for developing severe alcohol withdrawal.

Younger patients tended to have more severe withdrawal. The screening instrument the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) performed best for predicting the development of severe alcohol withdrawal (positive LR = 174, negative LR = 0.07).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Evan Wood, MD, PhD (BC Centre on Substance Use; University of British Columbia), had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. David Simel, MD (Durham Veterans Affairs Medical Center) provided invaluable guidance at all stages throughout the manuscript's design, development and revision. Dr. Simel also calculated the summary likelihood ratio results and standard mean differences using data provided by Dr. Wood. We thank the following colleagues: Greg Rowell, MSc, MSt (Clinical + Systems Transformation, Vancouver Coastal Health), and Ashwini Sreekanta, MSc (University of Oxford), for research and administrative assistance that was compensated or conducted as part of their regular paid positions with their respective organizations. We thank Jessica Jun, BSc (University of British Columbia), Lauren Adye White, BA, BSc (University of British Columbia), Lauren Gorfinkel, BSc (BC Centre on Substance Use), Dr. Brit Cooper-Jones, MD (BC Centre on Substance Use), Athena Huynh, BSc candidate (University of British Columbia), and Emily Wagner, MSc (BC Centre on Substance Use) for research and administrative assistance that was provided as part of their regular paid positions with the BC Centre on Substance Use. We thank authors of the included studies for additional unpublished information. We thank Drs. Joshua Briscoe, MD (Duke University Medical Center), Rebekah Jakel, MD, PhD (Durham Veterans Affairs Medical Center) and Kristen Shirey, MD (Duke University Medical Center) for their peer review of an earlier version of this manuscript for which they were not compensated.

Funding/Support: This research was undertaken, in part, thanks to funding from the Canada Research Chairs program through a Tier 1 Canada Research Chair in Inner City Medicine which supports Dr. Evan Wood. The ELEVATE grant: Irish Research Council International Career Development Fellowship – co-funded by Marie Curie Actions (ELEVATEPD/2014/6); and the European Commission grant (701698) supports Dr. Klimas. Dr. Ahamad is supported by a Canadian Institutes of Health Research Embedded Clinician Scientist Award. Funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Role of the Sponsor: The study was investigator-initiated and without external financial support other than granting agency salary awards as reported under Funding/Support.

REFERENCES

1. Peacock A, Leung J, Larney S, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction*. 2018 5 10. doi: 10.1111/add.14234. [Epub ahead of print].
2. Maldonado JR, Sher Y, Das S, et al. Prospective validation study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in medically ill inpatients: a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol Alcohol*. 2015;50(5):509–518. [PubMed: 25999438]
3. Doering-Silveira J, Fidalgo TM, Nascimento CLES, et al. Assessing alcohol dependence in hospitalized patients. *Int J Environ Res Public Health*. 2014;11(6):5783–5791. [PubMed: 24879488]
4. Rehm J, Anderson P, Manthey J, et al. Alcohol use disorders in primary health care: What do we know and where do we go? *Alcohol Alcohol*. 2016;51(4):422–427. [PubMed: 26574600]
5. McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. *J Neurol Neurosurg Psychiatry*. 2008;79(8):854–862. [PubMed: 17986499]

6. Erwin WE, Williams DB, Speir WA. Delirium tremens. *South Med J*. 1998;91(5):425–432. [PubMed: 9598848]
7. Trevisan LA, Boutros N, Petrakis IL, Krystal JH. Complications of alcohol withdrawal: pathophysiological insights. *Alcohol Health Res World*. 1998;22(1):61–66. [PubMed: 15706735]
8. Salottolo K, McGuire E, Mains CW, van Doorn EC, Bar-Or D. Occurrence, Predictors, and Prognosis of Alcohol Withdrawal Syndrome and Delirium Tremens Following Traumatic Injury. *Crit Care Med*. 2017;45(5):867–874. [PubMed: 28266937]
9. National Institute on Alcohol Abuse and Alcoholism. Rethinking drinking: alcohol and your health. Bethesda, MD: National Institutes of Health; 2016 NIH publication no. 15–3770 https://pubs.niaaa.nih.gov/publications/rethinkingdrinking/rethinking_drinking.pdf Published 2010. Revised May 2016 Accessed February 2, 2018.
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5™. 5th ed Arlington, VA: American Psychiatric Publishing, Inc; 2013.
11. Littleton J Neurochemical mechanisms underlying alcohol withdrawal. *Alcohol Health Res World*. 1998;22(1):13–24. [PubMed: 15706728]
12. Schuckit MA. Alcohol-use disorders. *Lancet*. 2009;373(9662):492–501. [PubMed: 19168210]
13. Goodson CM, Clark BJ, Douglas IS. Predictors of severe alcohol withdrawal syndrome: a systematic review and meta-analysis. *Alcohol Clin Exp Res*. 2014;38(10):2664–2677. [PubMed: 25346507]
14. Schmidt KJ, Doshi MR, Holzhausen JM, Natavio A, Cadiz M, Winegardner JE. Treatment of Severe Alcohol Withdrawal. *Ann Pharmacother*. 2016;50(5):389–401. [PubMed: 26861990]
15. Tsuang JW, Irwin MR, Smith TL, Schuckit MA. Characteristics of men with alcoholic hallucinosis. *Addiction*. 1994;89(1):73–78. [PubMed: 7755673]
16. Stephane M, Arnaout B, Yoon G. Alcohol withdrawal hallucinations in the general population, an epidemiological study. *Psychiat Res*. 2018;262:129–134.
17. Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. *CNS Drugs*. 2003;17(14):1013–1030. [PubMed: 14594442]
18. Wartenberg AA. Chapter 43: Management of Alcohol Intoxication and Withdrawal In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. *The ASAM Principles of Addiction Medicine*. 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:635–651.
19. Kim DW, Kim HK, Bae EK, Park SH, Kim KK. Clinical predictors for delirium tremens in patients with alcohol withdrawal seizures. *Am J Emerg Med*. 2015;33(5):701–704. [PubMed: 25745798]
20. Mirijello A, D'Angelo C, Ferrulli A, et al. Identification and management of alcohol withdrawal syndrome. *Drugs*. 2015;75(4):353–365. [PubMed: 25666543]
21. Eyer F, Schuster T, Pfab R, Felgenhauer N, Zilker T. Risk Assessment of Moderate to Severe Alcohol Withdrawal - Predictors for seizures and delirium tremens in the course of withdrawal. *Clin Toxicol*. 2011;49(3):201–202.
22. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med*. 2014;371(22):2109–2113. [PubMed: 25427113]
23. Babor TF, Higgins-Biddle JC. Brief intervention for hazardous and harmful drinking: a manual for use in primary care. Geneva, Switzerland: World Health Organization; 2001 http://apps.who.int/iris/bitstream/10665/67210/1/WHO_MSD_MSB_01.6b.pdf. Published 2001 Accessed February 2, 2018.
24. Kitchens JM. Does this patient have an alcohol problem? *JAMA*. 1994;272(22):1782–1787. [PubMed: 7966928]
25. Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*. 2005;330(7501):1179. [PubMed: 15894554]
26. Simel DL, Keitz S. Update: primer on precision and accuracy In: Simel DL, Rennie D, eds. *Rational Clinical Examination: The Evidence-Based Clinical Diagnosis*. New York, NY: McGraw-Hill; 2008:9–16.
27. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25. [PubMed: 14606960]

28. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol*. 2006;6:9. [PubMed: 16519814]
29. Management of Substance Abuse Unit. Global status report on alcohol and health 2014. Geneva, Switzerland: World Health Organization; 2016 http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf?ua=1. Published April 2014 Accessed December 8, 2016.
30. Caetano R, Clark CL, Greenfield TK. Prevalence, trends, and incidence of alcohol withdrawal symptoms: analysis of general population and clinical samples. *Alcohol Research and Health*. 1998;22(1):73.
31. Simel DL, Easter J, Tomlinson G. Likelihood ratios, sensitivity, and specificity values can be back-calculated when the odds ratios are known. *J Clin Epidemiol*. 2013;66(4):458–460. [PubMed: 23021858]
32. Williams D, Lewis J, McBride A. A comparison of rating scales for the alcohol-withdrawal syndrome. *Alcohol Alcohol*. 2001;36(2):104–108. [PubMed: 11259205]
33. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 The Cochrane Collaboration; 2011 Available from: <http://training.cochrane.org/handbook> Updated March 2011 Accessed December 8, 2016.
34. *Comprehensive Metaanalysis Version 2.0*. Englewood, NJ: Biostat; 2005. In.
35. Simel DL, Bossuyt PM. Differences between univariate and bivariate models for summarizing diagnostic accuracy may not be large. *J Clin Epidemiol*. 2009;62(12):1292–1300. [PubMed: 19447007]
36. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188. [PubMed: 3802833]
37. Cummings P Arguments for and against standardized mean differences (effect sizes). *Arch Pediatr Adolesc Med*. 2011;165(7):592–596. [PubMed: 21727271]
38. Cohen J *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988:20–26.
39. Wetterling T, Weber B, Depfenhart M, Schneider B, Junghanns K. Development of a rating scale to predict the severity of alcohol withdrawal syndrome. *Alcohol Alcohol*. 2006;41(6):611–615. [PubMed: 16980710]
40. Wetterling T, Kanitz RD, Besters B, et al. A new rating scale for the assessment of the alcohol-withdrawal syndrome (AWS scale). *Alcohol Alcohol*. 1997;32(6):753–760. [PubMed: 9463730]
41. Kraemer KL, Mayo-Smith MF, Calkins DR. Independent clinical correlates of severe alcohol withdrawal. *Subst Abus*. 2003;24(4):197–209. [PubMed: 14574086]
42. Dolman JM, Hawkes ND. Combining the audit questionnaire and biochemical markers to assess alcohol use and risk of alcohol withdrawal in medical inpatients. *Alcohol Alcohol*. 2005;40(6):515–519. [PubMed: 16103035]
43. Pecoraro A, Ewen E, Horton T, et al. Using the AUDIT-PC to predict alcohol withdrawal in hospitalized patients. *J Gen Intern Med*. 2014;29(1):34–40. [PubMed: 23959745]
44. Kapur JH, Rajamanickam V, Fleming MF. Can the blood alcohol concentration be a predictor for increased hospital complications in trauma patients involved in motor vehicle crashes? *Int J Environ Res Public Health*. 2010;7(3):1174–1185. [PubMed: 20617025]
45. Denis CM, Gelernter J, Hart AB, Kranzler HR. Inter-observer reliability of DSM-5 substance use disorders. *Drug Alcohol Depend*. 2015;153:229–235. [PubMed: 26048641]
46. Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend*. 2003;71(1):7–16. [PubMed: 12821201]
47. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353–1357. [PubMed: 2597811]
48. Pierucci-Lagha A, Gelernter J, Chan G, et al. Reliability of DSM-IV diagnostic criteria using the semi-structured assessment for drug dependence and alcoholism (SSADDA). *Drug Alcohol Depend*. 2007;91(1):85–90. [PubMed: 17590536]

49. Lee JH, Jang MK, Lee JY, et al. Clinical predictors for delirium tremens in alcohol dependence. *J Gastroenterol Hepatol*. 2005;20(12):1833–1837. [PubMed: 16336440]
50. Berggren U, Fahlke C, Berglund KJ, Blennow K, Zetterberg H, Balldin J. Thrombocytopenia in early alcohol withdrawal is associated with development of delirium tremens or seizures. *Alcohol Alcohol*. 2009;44(4):382–386. [PubMed: 19293148]
51. Fiellin DA, O'Connor PG, Holmboe ES, Horwitz RI. Risk for delirium tremens in patients with alcohol withdrawal syndrome. *Subst Abus*. 2002;23(2):83–94. [PubMed: 12444353]
52. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282(11):1061–1066. [PubMed: 10493205]
53. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev*. 2010(3):CD005063.
54. Knight E, Lappalainen L. Clinical Institute Withdrawal Assessment for Alcohol-Revised might be an unreliable tool in the management of alcohol withdrawal. *Canadian Family Physician*. 2017;63(9):691–695. [PubMed: 28904034]
55. Mayo-Smith MF. Pharmacological management of alcohol withdrawal: A meta-analysis and evidence-based practice guideline. *JAMA*. 1997;278(2):144–151. [PubMed: 9214531]
56. Maldonado JR. Novel algorithms for the prophylaxis and management of alcohol withdrawal syndromes-beyond benzodiazepines. *Crit Care Clin*. 2017;33(3):559–599. [PubMed: 28601135]
57. Alcohol withdrawal syndrome: preventive measures. *Prescrire Int*. 2015;24(166):300–301. [PubMed: 26788581]
58. Brathen G, Bjerve KS, Brodtkorb E, Bovim G. Validity of carbohydrate deficient transferrin and other markers as diagnostic aids in the detection of alcohol related seizures. *J Neurol Neurosurg Psychiatry*. 2000;68(3):342–348. [PubMed: 10675217]
59. Monte R, Rabunal R, Casariego E, Bal M, Pertega S. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J Intern Med*. 2009;20(7):690–694. [PubMed: 19818288]

Box 1.
Definitions of at-risk drinking and alcohol withdrawal syndrome.

Condition	Definition
At-risk / Heavy Alcohol Use	Alcohol consumption that exceeds more than 4 drinks on any day or 14 drinks per week for men, or more than 3 drinks on any day or 7 drinks per week for women.
Alcohol Withdrawal [*] Syndrome (A, B, C & D required for diagnosis)	A) Cessation of (or reduction in) alcohol use that has been heavy and prolonged B) Two (or more) of the following, developing within several hours to a few days after cessation of (or reduction in) alcohol use described in Criterion A: autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, generalized tonic-clonic seizures C) The signs and symptoms in Criterion B cause significant distress or impairment in social, occupational, or other important areas of functioning D) The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance
Delirium ^{**} Tremens	A patient must meet the criteria for Alcohol Withdrawal (as described above), as well as Delirium (as follows): A) A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment) B) The disturbance developed over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day C) An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuo-spatial ability, or perception) D) The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of severely reduced level of arousal, such as coma E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of alcohol withdrawal
Alcohol Withdrawal [*] Seizure	Grand mal or generalized tonic-clonic seizures (typically the generalized tonic-clonic type, which is characterized by rhythmic, yet jerking movement, especially of the limbs)

* Definition according to the National Institute on Alcohol Abuse and Alcoholism

** Definitions according to the Diagnostic and Statistical Manual of Mental Disorders 5. Note “severe” alcohol withdrawal is a clinical diagnosis for which a number of definitions were used in the studies reviewed in this article (see eContent eTable 1).

Box 2.
The Prediction of Alcohol Withdrawal Severity
Scale (PAWSS)²

Part A: Threshold criteria:
1. Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days OR did the patient have a +BAL upon admission?
Part B: Based on patient interview:
2. Have you ever experienced previous episodes of alcohol withdrawal?
3. Have you ever experienced alcohol withdrawal seizures?
4. Have you ever experienced delirium tremens or DT?
5. Have you ever undergone alcohol rehabilitation treatment? (i.e., in-patient or out-patient treatment programs or AA attendance)
6. Have you ever experienced blackouts?
7. Have you combined alcohol with “downers” like benzodiazepines or barbiturates during the last 90 days?
8. Have you combined alcohol with any other substance of abuse during the last 90 days?
Part C: Based on clinical evidence:
9. Was the patient’s blood alcohol level (BAL) on presentation > 200?
10. Is there evidence of increased autonomic activity (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea)

KEY POINTS.

Question: Severe alcohol withdrawal syndrome (SAWS) can have devastating consequences, but how to predict which patients will be affected in acute care settings is not clear.

Findings: Individual symptoms and signs are not useful for predicting SAWS. Assessment tools incorporating combinations of symptoms and signs better predict which patients are at high risk of SAWS.

Meaning: The most effective method for predicting SAWS in acute care settings is use of a risk assessment tool that combines findings from a patient's history and clinical examination.

Table 1.

Summary Measures for Categorical Findings that predict Seizure, Delirium Tremens and Severe Alcohol Withdrawal Syndrome (see eTable 4 for results from individual studies)

Finding	Studies	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI), I ²	LR- (95% CI), I ²
Risk Factors					
<u>Demographics</u>					
Sex (male) ^d	5 ^{8,43,51,58,59}	0.79 (0.68–0.87)	0.39 (0.27–0.51)	1.3 (1.0–1.7) 95%	0.58 (0.40–0.84) 71%
Race-ethnicity (white) ^a	3 ^{8,43,51}	0.69 (0.55–0.80)	0.34 (0.21–0.51)	1.1 (1.0–1.2) 0%	0.84 (0.71–0.99) 0%
<u>Psychiatric History</u>					
Substance-use disorder, other than alcohol ^a	1 ²	0.07 (0.02–0.22)	0.99 (0.97–1.0)	6.4 (1.2–34)	0.94 (0.85–1.0)
Any psychiatric disorder ^a	1 ²	0.76 (0.58–0.88)	0.77 (0.72–0.81)	3.3 (2.5–4.4)	0.31 (0.16–0.60)
Mood disorders ^a	1 ²	0.48 (0.31–0.65)	0.84 (0.80–0.87)	3.0 (1.9–4.7)	0.62 (0.43–0.88)
Anxiety disorders ^a	1 ²	0.07 (0.02–0.22)	0.97 (0.95–0.98)	2.6 (0.60–11)	0.96 (0.87–1.1)
<u>Alcohol Withdrawal History</u>					
History of Delirium Tremens ^b	3 ^{49,51}	0.33 (0.23–0.46)	0.88 (0.77–0.94)	2.9 (1.7–5.2) 42%	0.78 (0.67–0.91) 0%
Number of epileptic seizures at diagnosis of minor AWS ^c	1 ⁵⁹				
3 ^c seizures	...	...	...	2.8 (1.4–5.9)	...
1 – 2 ^c seizures	...	...	...	1.6 (1.4–2.2)	...
0 ^c seizures	...	...	...	...	0.63 (0.50–0.78) ...
History of Severe-/ alcohol withdrawal syndrome ^c	2 ^{51,59}	0.24–0.78	0.73–0.91	1.5–2.0	0.64–0.91
History of seizures ^e	2 ^{50,51}	0.00–0.38	0.80–0.91	0.47–1.7	0.83–1.1
<u>Signs</u>					
Systolic Blood Pressure 140mmHg ^f	3 ^{49,51,59}	0.42 (0.33–0.51)	0.73(0.59–0.84)	1.7 (1.3–2.3) 28%	0.78 (0.69–0.89) 0%
<u>Laboratory findings</u>					
Blood Alcohol Concentration 200mg/dl ^g	1 ⁴⁴	0.48(0.43–0.53)	0.86(0.85–0.87)	3.5 (3.0–4.0)	0.61 (0.55–0.67)
Blood urea nitrogen (>26 mg/dL at Admission) ^c	1 ⁴⁹	0.28(0.15–0.46)	0.92(0.86–0.96)	3.3 (1.4–7.6)	0.79 (0.63–1.0)

Finding	Studies	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI), I ²	LR- (95% CI), I ²
Thrombocytopenia (<150 ×10 ³ /μL) ^c	1 ⁵⁰	0.70(0.40–0.89)	0.69(0.64–0.74)	2.2 (1.4–3.4)	0.44 (0.17–1.1)
Composite measures					
Prediction of Alcohol Withdrawal Severity Scale (PAWSS) 4 ^{aj}	1 ²	0.93(0.77–0.99)	0.99(0.98–0.99)	174 (43–696)	0.07 (0.02–0.26)
Independent clinical correlates 5 ^{c,h}	1 ⁴¹	0.13(0.07–0.23)	1.0(0.98–1.0)	27 (3.5–209)	0.88 (0.80–0.96)
Luebeck Alcohol Risk Scale (LARS)-10 9 ^{ak}	1 ³⁹	0.95(0.77–0.99)	0.93(0.88–0.94)	12 (5.8–27)	0.05 (0.0–0.37)
Rating scale for the assessment of the alcohol-withdrawal syndrome 10 ^{al}	1 ⁴⁰	0.78(0.59–0.90)	0.90(0.85–0.93)	7.4 (4.8–11)	0.25 (0.12–0.50)
Independent clinical correlates = 4 ^{c,h}	1 ⁴¹	0.25(0.16–0.36)	0.96(0.92–0.98)	6.8 (3.1–15)	0.78 (0.68–0.89)
History of a SAWS and at least 1 adverse clinical feature ^c	1 ⁵¹	0.40(0.20–0.64)	0.91(0.79–0.96)	4.5 (1.5–14)	0.66 (0.43–1.0)
Abnormal vital sign ^{ai}	1 ³⁹	0.37(0.28–0.47)	0.82 (0.82–0.83)	2.1 (1.7–2.7)	0.76 (0.66–0.88)

Abbreviations: LR, likelihood ratio; AWS, alcohol withdrawal syndrome, SAWS, severe alcohol withdrawal syndrome; (...) results are for stratum specific serial LR so that the sensitivity, specificity, and LR do not apply

^aCondition(s) under study: Severe Alcohol Withdrawal Syndrome

^bCondition(s) under study: Delirium Tremens

^cCondition(s) under study: Delirium Tremens

^dCondition(s) under study: Seizure,⁵⁸ Delirium Tremens,⁵⁹ Alcohol Withdrawal Syndrome,^{43,51} and Severe Alcohol Withdrawal Syndrome³⁹

^eCondition(s) under study: Delirium Tremens,³⁶ and Seizure;^{50,51} if a study reported both Delirium Tremens and seizures, data for Delirium Tremens only were pooled

^fCondition(s) under study: Delirium Tremens; pooled from 3 studies with thresholds of 140 mmHg,⁴⁹ 145 mmHg,⁵¹ and 150 mmHg⁵⁹

^gCondition(s) under study: Alcohol Withdrawal Syndrome

^hThe six independent correlates were: use of a morning eye-opener, initial CIWA-Ar score ≥ 10, AST ≥ 80 U/L, past benzodiazepine use, history of delirium tremens, and ≥ 2 prior alcohol treatments. Scoring categories were: low-risk (0–2 correlates present), moderate risk (3 correlates present) and high-risk (4–6 correlates present).

ⁱAdmission SBP < 80 mm Hg, or respiratory rate < 10 and > 29 breaths/min, or heart rate > 120 beats/min.

^jPAWSS is a 10-item scale (possible score range: 0–10) for predicting risk of Alcohol Withdrawal Syndrome in hospitalized medically ill patients. A score of 4 or greater is considered to identify those at high risk. See Box 2 for a complete list of the 10 items.

^kLARS-10 is a 10-item rating scale (possible score range: 0–14) to predict the severity of alcohol withdrawal syndrome. A score of 9 or greater is considered to identify patients with severe AWS.

⁷Rating scale for assessment of the alcohol-withdrawal syndrome (AWS Scale) is an 11-item rating scale, in which each item is scored from 0–3 for somatic symptoms or 0–4 for mental symptoms (total possible score range: 0–38). A score of 5 or less is considered to identify patients with mild AWS; a score of 6–9 is considered to identify patients with moderate AWS; and a score of 10 or greater is considered to identify patients with severe AWS.

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Table 2.

Summary Measures for Continuous Findings of Seizure, Delirium Tremens and Alcohol Withdrawal Syndrome (see eTable 5 for results from individual studies)

Finding	Studies	Participants	SMD (95% CI) or range
		Risk Factor	
Age ^a	4 ^{39,43,58,59}	1250	−0.27 (−0.49 to −0.05)
		Signs	
Systolic blood pressure ^{b,d}	2 ^{50,59}	697	−0.70 to 0.38 ^c
Diastolic blood pressure	2 ^{50,59}	637	−0.47 to 0.32 ^c
Heart rate ^{b,d}	2 ^{50,59}	697	0.01 to 0.06 ^c
		Laboratory findings	
Gamma-glutamyl transpeptidase (GGT) ^b	2 ^{50,59}	637	0.03 to 1.41 ^c
Aspartate aminotransferase (AST) ^b	2 ^{50,59}	637	0.07 to 0.88
Potassium ^b	2 ^{50,59}	637	−0.73 to −0.20 ^c
Alanine aminotransferase (GGT) ^b	2 ^{50,59}	637	0.04 to 0.18
Platelet count ^b	2 ^{50,59}	637	−0.59 to −0.35 ^c

Abbreviations: SMD, standardized mean difference

^aConditions under study: Seizure,⁵⁸ Delirium Tremens⁵⁹ and Severe/ Alcohol Withdrawal Syndrome^{8,43}

^bConditions under study: Delirium Tremens

^cRange of means for participants with the condition (positives)

^dOne study did not report standard deviations (SD)⁵⁸; therefore, the SMD was calculated for two studies only^{59, 43}