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Transzlációs és klinikai farmakológia

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Improving outcomes in acute life threatening emergencies

Ph.D. thesis

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"What do you have that you didn't receive…?"

Bible, 1 Corinthians 4:7b

DOI:10.14753/SE.2025.3197

TABLE OF CONTENS

DOI:10.14753/SE.2025.3197

DOI:10.14753/SE.2025.3197

1. LIST OF ABBREVIATIONS

APACHE	acute physiology and chronic health evaluation
art	arterial
AG	anion gap
AKI	acute kidney injury
BES	balanced electrolyte solutions
bicarb	bicarbonate
BLUE	bedside lung ultrasound in emergency
cap	capillary
CI	confidence interval
CIL and CIU	confidence intervals lower and upper
CPR	cardiopulmonary resuscitation
CXR	chest X-ray
CT	computer tomography
DKA	diabetic ketoacidosis
DM	diabetes mellitus
ECG	electrocardiogram
ED	emergency department
Exc	exclusion
ESKD	end stage kidney disease
FATE	focus assessed transthoracic echocardiography
Fig	figure
GCS	Glasgow coma scale
glu	glucose
GRADE	grading of recommendations, assessment, development and evaluation
HHS	hyperglycaemic hyperosmolar states, hyperosmotic hyperglycemic non-ketotic syndrome
ICU	intensive care unit
Inc	inclusion
IVC	inferior vena cava
LOS	length of stay
LUS	lung ultrasound

LV	left ventricule
MD	mean difference
MeD	median difference
MET	medical emergency team
Obs	observational study
OR	odds ratio
PL	Plasma-Lyte
pla	plasma
PICO	patients, intervention, control, outcome
PoCUS	point-of-care ultrasound
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	international prospective register of systematic reviews
RCT	randomized controlled trial
RL	Ringer's lactate
RoB 2	revised tool for risk of bias in randomized trials
ROBINS-I	risk of bias in non-randomized studies of interventions
RR	respiratory rate
RRT	rapid response team
RV	right ventricule
se	serum
SAT	peripherial oxygen saturation
SD	standard deviation
y	years

DOI:10.14753/SE.2025.3197

2. STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is to implement new approaches and make unproven conventional treatments obsolete by providing scientific evidence that could improve outcomes in emergency care.

I aim to provide scientific evidence to prove the above and implement evidence-based patient care on a broader scale in my professional environment.

My specific goals include investigating the utility of PoCUS in patients admitted with acute onset dyspnea and assessing the efficacy of BES in adult patients treated with DKA.

2.2 Scientometrics

Number of all publications:	3	
Cumulative IF:	10.8	
Av IF/publication:	3.6	
Ranking (Sci Mago):	D1: 1	Q1: 2
Number of publications related to the subject of the thesis:	2	
Cumulative IF:	7.8	
Av IF/publication:	3.9	
Ranking (Sci Mago):	D1: 1	Q1: 1
Number of citations on Google Scholar:	28	
Number of citations on MTMT (independent):	16	
H-index:	1	

DOI:10.14753/SE.2025.3197

2.3 Future plans

My future plans include the broader dissemination of PoCUS as a relatively new diagnostic and decision support modality and its introduction to colleagues. This will require appropriate infrastructure development and a significant amount of training.

Furthermore, it is essential that the care of adult patients admitted to the hospital for DKA should not be based on the experience of an insufficient number of previous studies but that guidelines should be able to use the results of our research in the future.

DOI:10.14753/SE.2025.3197

3. SUMMARY OF THE PH.D.

Timely, accurate, and adequate diagnostic and therapeutic interventions in emergency care are the cornerstones of saving lives. Accordingly, my research has sought to answer how to optimise care of the patients treated with dyspnea, what type of fluid resuscitation should be performed in adults with DKA.

Acute onset dyspnea is one of the most frequent causes of hospital admission and calls for the rapid response team, where the mortality rate remains high. Differential diagnosis remains challenging, which can lead to delayed treatment. Our main objective was to examine whether combining PoCUS with conventional modalities improves clinical outcomes in patients with acute onset dyspnea.

In my first published paper, which was a systematic review and meta-analysis, we have shown that patients admitted with acute onset dyspnea and managed with PoCUS have a significantly shorter time to diagnosis, time to treatment, higher rate of receiving appropriate treatment, and decreased stay in ICU compared to conventional approaches. However, using PoCUS has a limited influence on 30-day and in-hospital mortality and has no relevant effect on the 30-day re-admission rate.

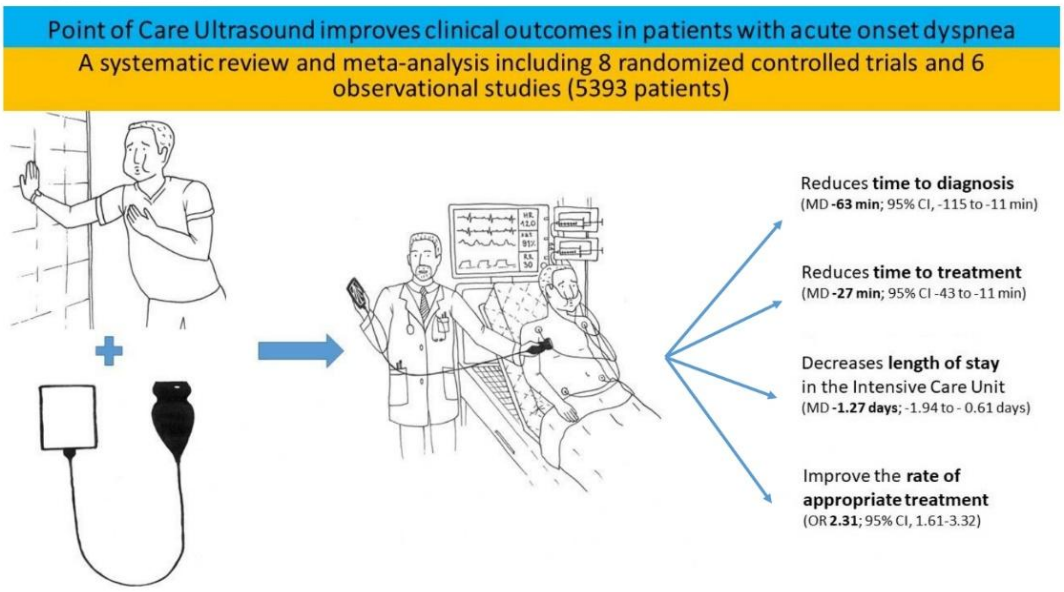
DKA is a life-threatening condition based on severe dehydration, metabolic acidosis, and hyperglycemia. One of the cornerstones of treatment is early, adequate fluid resuscitation. Traditionally, the 0.9% NaCl solution is the recommended first choice for fluid resuscitation, but it can lead to hyperchloremic metabolic acidosis and enhanced inflammatory response. In contrast, BES may reduce the time to resolution of DKA. Evidence was still controversial on this topic. We aimed to perform a meta-analysis of all published studies in the field and provide further evidence regarding the best type of fluid for resuscitation in DKA.

In my second published paper, which was also a systematic review and meta-analysis, we revealed that BES resolved DKA faster than 0.9% saline. Furthermore, patients treated with 0.9% saline may have higher serum sodium and chloride post-resuscitation levels and lower serum bicarbonate levels.

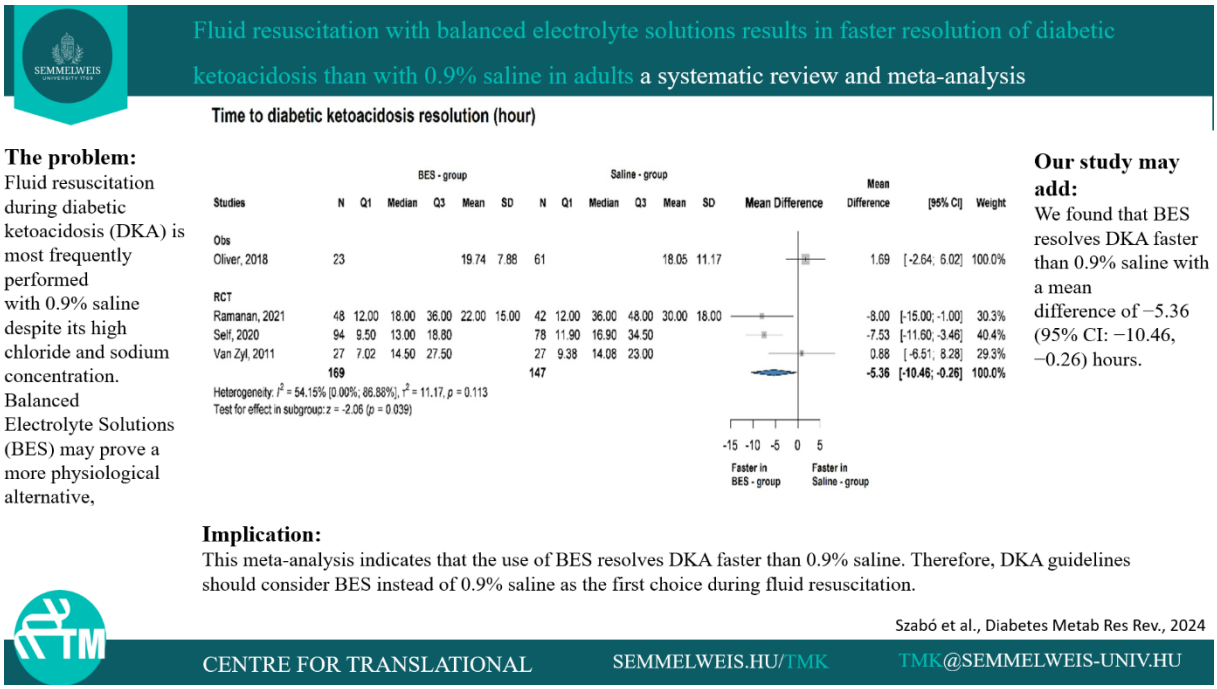
DOI:10.14753/SE.2025.3197

4. GRAPHICAL ABSTRACT

4.1 Study I.



4.2 Study II.



DOI:10.14753/SE.2025.3197

5. INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

The focus of my research has been on how to improve outcomes in acute life-threatening emergencies, especially evaluating the utility of PoCUS in patients treated with acute onset dyspnea and finding the best type of infusion in adult patients admitted with DKA.

5.1.2 What is the problem to solve?

Patients with shortness of breath often do not have time to wait for conventional testing methods, and in patients hospitalised for DKA, inadequate fluid supplementation can cause serious side effects.

5.1.3 What is the importance of the topic?

5.1.3.1 Study I.

Acute-onset dyspnea is one of the most common symptoms for which patients visit the Emergency Department (ED) (1-4). In the United States, dyspnea is the main reason for four to five million ED visits annually (4), representing up to 50% of patients admitted to acute tertiary care hospitals (5). In the Asia–Pacific region, 5% of all ED presentations are due to dyspnea (6). In addition to its high incidence, the 30-day mortality rate of these patients remains relatively high (8–13%) (7, 8). Therefore, rapid and appropriate diagnosis of the underlying pathology is of utmost importance for prompt and adequate treatment (9).

However, differential diagnosis is often challenging (10, 11). Most physicians mainly rely on conventional diagnostic modalities, such as medical history, physical examination, chest X-ray (CXR), electrocardiogram (ECG), and standard laboratory tests (12). Even given all these tests, some studies have raised doubts about the diagnostic accuracy of these conventional approaches, especially in the critically ill patient population (13, 14).

5.1.3.2 Study II.

Diabetic ketoacidosis (DKA) is an acute life-threatening condition requiring 30 admissions per 1000 people with diabetes mellitus a year (15). The classic clinical triad in DKA is hyperglycaemia, ketosis, and acidosis (16, 17). Although overall mortality has decreased to less than 1% over the past 2 decades, the last few years have shown a tendency towards a growing number of cases (15). Fluid therapy, in addition to the control of electrolyte balance and insulin therapy, is one of the cornerstones of DKA management (18, 19). The most frequently applied crystalloid solution in DKA treatment is 0.9% sodium chloride (saline), also recommended in several guidelines (20-23). However, the chloride and sodium content of 0.9% saline is 154 mEq/L, which is substantially higher than the physiologic concentrations in humans (98–111 mEq/L for chloride and 135–145 mmoL/L for sodium) (17, 24). Although the clinical consequences of administering large volumes of 0.9% saline are currently unclear, it may theoretically lead to hyperchloremic metabolic acidosis with all its associated complications (e.g., immune dysfunction, acute kidney injury (AKI), gastrointestinal impairment) (25-27). Hyperchloraemia in DKA patients has also been associated with a longer time to DKA resolution and longer inhospital length of stay (LOS) (28). In contrast, balanced electrolyte solutions (BES) have more physiological properties as they contain less chloride and have lower osmolarity. Hence, they may be a better alternative for fluid resuscitation in patients admitted with DKA (29-31).

5.1.4 What would be the impact of our research results?

5.1.4.1 Study I.

The use of Point-of-care ultrasound (PoCUS) has gained increasing popularity in several domains of acute patient management, including acute onset dyspnea (11, 32). There is an increasing body of evidence demonstrating that the accuracy of PoCUS is comparable to the current imaging reference standard CXR in general (33) as well as in specific conditions, such as pneumonia (34), acute decompensated heart failure (33), pleural effusion (35), pneumothorax (36) and pulmonary embolism (37). PoCUS has other advantages, such as being free from ionizing radiation, and most importantly can be performed in real-time at the bedside (33, 38). Additionally, PoCUS can answer a broad

spectrum of remaining diagnostic questions and may also help to optimize and personalize therapy (39). However, very few trials have examined meaningful clinical outcomes related to PoCUS usage to date (40) and the results on outcome measurements were heterogeneous (41).

Therefore, we conducted a high-quality, comprehensive systematic review and meta-analysis that included the most recent publications that reported clinical outcomes with the use of PoCUS in patients who developed acute onset dyspnea. In addition to the existing diagnostic accuracy studies (33-37, 42), our main objective, as a new insight to this field, was to investigate how PoCUS improves clinical endpoints in patients with acute onset dyspnea.

5.1.4.2 Study II.

Several randomized controlled trials (RCTs), systematic reviews, and meta-analyses concerning the most suitable infusion in the general critical care population exist. However, only some evaluate patients specifically treated for DKA, and the results remain controversial (43-51). It may be reasonably stated that although international guidelines still recommend 0.9% saline as the fluid of choice when treating DKA, this recommendation stands only because very few studies have been published comparing BES with 0.9% saline in adults admitted with DKA, and because 0.9% saline is the traditional choice, is readily available, and clinicians have much experience using it (20-23). The latest meta-analysis on this topic was conducted in 2022, and the use of BES in DKA was associated with faster rates of DKA resolution compared to 0.9% saline (based on pooled small randomized trials). Still, there are two other important studies published that year that were not included in the analysis (17, 52, 53).

Therefore, our main aim was to evaluate the effects of BES compared with 0.9% saline in adult patients admitted with DKA.

DOI:10.14753/SE.2025.3197

6. OBJECTIVES

6.1 Investigating the clinical value of Point of Care Ultrasound in patients with acute onset dyspnea

The early, appropriate management of acute onset dyspnea is important but often challenging. The aim of this study was to investigate the effects of the use of Point of Care Ultrasound versus conventional management on clinical outcomes in patients with acute onset dyspnea.

6.2 Investigating the efficacy of balanced electrolyte solutions in patients admitted with diabetic ketoacidosis

Fluid resuscitation is the cornerstone of early management in DKA. Guidelines recommend 0.9% saline as first line choice, although this infusion can cause hyperchloremic metabolic acidosis and impaired renal function. In contrast in BES electrolyte levels are more physiological thereby theoretically it can improve acid base balance. Evidence is still controversial on this topic, therefore in our systhematic review and meta-analysis we compared the efficacy of 0.9 % saline versus Balanced Electrolyte Solutions in resolving diabetic ketoacidosis in adults.

7. METHODS

7.1 Study I.

7.1.1 Protocol registration and search strategy

The protocol was prospectively registered via the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42021284070. There was no deviation from the protocol. We report our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (54).

We systematically searched MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for eligible articles on 14 October, 2021. We applied “title, abstract, author, keyword” filters in EMBASE—no other filters were used. We did not use any restrictions or limitations based on language or publication date. We also scanned the reference lists of included studies and the cited articles in Google Scholar. The detailed search key was the following:

EMBASE:

('point of care'/exp OR 'point of care' OR portable OR bedside OR 'bed side' OR handheld OR 'hand held' OR 'hand carried' OR pocket OR mobile) AND (ultrasoun* OR ultrason* OR sonogr* OR echo*) AND (pneumo* OR bronchopneumon* OR pleuropneumon* OR chylothora* OR hemothora* OR haemothora* OR hydropneumothora* OR hydrothora* OR ((pulmo* OR 'lung'/exp OR lung OR 'vein'/exp OR vein) AND (edem* OR oedem* OR 'congestion'/exp OR congestion OR embol* OR thromb*)) OR (('heart'/exp OR heart OR cardiac OR circula* OR resp*) AND ('failure'/exp OR failure OR 'distress'/exp OR distress OR insufficien*)) OR dyspn* OR breathless* OR (short* AND of AND ('breath'/exp OR breath)))

Pubmed and CENTRAL:

(("point of care" OR point-of-care OR portable OR bedside OR bed-side OR handheld OR hand-held OR hand-carried OR pocket OR mobile) AND (ultrasoun* OR ultrason*

OR sonogr* OR echo*)) AND (pneumo* OR bronchopneumon* OR pleuropneumon* OR chylothora* OR hemothora* OR haemothora* OR hydropneumothora* OR hydrothora* OR ((pulmo* OR lung OR vein) AND (edem* OR oedem* OR congestion OR embol* OR thromb*)) OR ((heart OR cardiac OR circula* OR resp*) AND (failure OR distress OR insufficien*)) OR dyspn* OR breathless* OR (short* of breath))

7.1.2 Selection process and data collection

Only randomized controlled trials (RCTs), and prospective and retrospective cohort studies were eligible for inclusion. Editorials, review articles, case reports, case series, conference abstracts, non-peer-reviewed articles and animal experiments were excluded. The selected studies had to match our previously defined PICO (Patients, Intervention, Control, Outcome) framework:

- P: Adults and children who were admitted to the ED or to the Intensive Care Unit (ICU), or to another inpatient setting because of acute onset or worsening dyspnea were eligible. We also included studies enrolling patients who developed shortness of breath from unknown etiologies and were already hospitalized. Studies reporting on trauma-induced acute onset dyspnea, or pregnancy were excluded.

- I: The examined intervention was PoCUS use on its own or in combination with conventional diagnostic measures. If PoCUS was applied in combination with conventional methods, the endpoints in each case should be able to be evaluated separately from the control arm. There were no restrictions on the type of PoCUS protocols.

- C: Control group included conventional diagnostic methods, such as taking the patients' medical history, physical examination, ECG, blood gas and different laboratory analyses, echocardiography, CXR, or computer tomography (CT).

- O: For the primary outcomes, we defined time to diagnosis (measured in minutes from admission or first medical contact until initial diagnosis was made), time to treatment (assessed as the previous point until the treatment was initiated) and

length of stay which was evaluated in the following three subgroups: in-hospital LOS, LOS in the ED and LOS in the ICU. The secondary outcomes were the following: mortality (in-hospital and 30-day), rate of appropriate treatment and 30-day re-admission rate.

- After the removal of duplicates using a reference management software (EndNote X9, Clarivate Analytics), two review authors (G.S. and C.S.) independently screened titles, abstracts, and then the full texts against predefined eligibility criteria.

Cohen's kappa coefficient (κ) was calculated (by G.S. and C.S.) to measure inter-rater reliability during the selection process, where values 0.01–0.20 indicate slight, 0.21–0.40 indicate fair, 0.41–0.60 indicate moderate, 0.61–0.80 indicate substantial, and 0.81–1.00 indicate almost perfect or perfect agreement. Discrepancies were resolved by two other review authors (Z.M. and M.R.).

Based on the consensus of methodological and clinical experts, we created a standardized data collection sheet. Data on the first author, publication year, countries, study design, number of patients in each group and their baseline characteristics (including age and gender), type of PoCUS protocol, examiners' practice and the available primary and secondary outcome parameters were extracted by two independent review authors (G.S. and C.S.) using our standardized data collection form in Microsoft Excel. There were no overlapping populations or duplicate data.

7.1.3 Risk of bias and quality assessment

The risk of bias was assessed based on the recommendations of the Cochrane Collaboration. Two independent review authors (G.S. and C.S.) did the assessment, and an independent third investigator resolved any disagreements (F.D.). For RCTs the RoB 2 tool (revised tool for Risk of Bias in randomized trials) was used, whereas for the cohorts, we used the ROBINS-I tool (Risk Of Bias in Non-randomized Studies of Interventions) (55, 56).

Publication bias was assessed by visual inspection of the Funnel plots and the leave-one-out sensitivity analyses (see original publication's Additional Figs. 2 and 3).

The quality assessment of the included studies was performed with GRADE-Pro (Grading of Recommendations, Assessment, Development and Evaluation–Pro) based on the recommendations of the Cochrane Collaboration (57). A detailed description of the quality assessment and risk of bias process can be found in the original publication's Additional Tables 1, 2, 3.

7.1.4 Statistical analysis

If there were at least three studies for an outcome, a metaanalysis was performed, and the results displayed in forest plots. For continuous outcomes, pooled mean differences (MDs), and for dichotomous variables, pooled odds ratios (ORs) along with their 95% confidence interval (CI), were calculated to investigate the differences between the compared arms. A random effect model was used for meta-analyses.

If the study number for the given outcome was over five, the Hartung–Knapp adjustment (58, 59) was applied.

In all instances, raw data were used: in the case of binary data, number of event and non-event, and in the case of continuous data, mean and standard deviation (SD). If the mean and SD were not reported in the article, we estimated them from the medians, quartiles, minimum and maximums using the Luo (60) and Shi (61) methods.

To estimate the heterogeneity variance measure, $\tau 2$ was applied estimated with the Q profile method. Statistical heterogeneity across trials was assessed by means of the Cochrane Q test, and the I2 values, where $p < 0.1$ was considered as statistically significant. Due to the low number of available studies, the Egger's test for the small-study effect could not be performed.

Outlier and influence analyses were carried out following the recommendations of Harrer et al. (62). All statistical analyses were performed with R (R Core Team, v4.1.1) (63) using the meta (Schwarzer 2022, v5.2.0) and dmetar (Cuijpers, Furukawa, and Ebert 2020, v0.0.9000) packages (64, 65).

7.2 Study II.

7.2.1 Protocol registration, search strategy, and study selection

Our systematic review and meta-analysis was performed according to our protocol registered in the International Prospective Register of Systematic Reviews on 27 November 2021 (PROSPERO; no. CRD42021293248). The results are reported following the PRISMA guidelines (54). The PRISMA checklist can be found in the original publication's Supplementary material (Additional File 3.).

We searched Medline, EMBASE and Cochrane from inception to 27 December 2021 for appropriate trials (66). The detailed search key is depicted in the original publication's Supplementary material (Additional File 3.). Per the recommendations of the Cochrane Collaboration, two authors (G.S. and C.S.) independently and separately screened the results for eligible records. After a discussion with the two authors, all disagreements were resolved by a consensus with a senior author (Z. M.). First, we screened titles and abstracts for eligibility, and then the full texts of suitable studies were reviewed. No language restrictions were applied. Reference lists of included articles and Google Scholar for cited studies were also scanned.

7.2.2 Eligibility criteria and outcomes

Randomized controlled trials and prospective and retrospective cohort studies comparing BES with 0.9% saline in patients treated with DKA were included. The exclusion criteria were editorials, review articles, case reports, case series, conference abstracts, and non-peer-reviewed articles. Animal studies were also deemed ineligible; furthermore, we rejected studies that assessed pregnant women, children, and patients with hyperglycaemic hyperosmolar states (HHS) due to different physiological and pathophysiological conditions. Infusions considered to be BES were Plasma-Lyte, Ringer's lactate, Isolyte, Sterofundin, Ringerfundin B Braun and Hartmann's solution (BES – group), while the comparator was always 0.9% saline (Saline – group). All the detailed inclusion and exclusion criteria are presented in the original publication's Supplementary material (Additional File 2.).

Our primary outcome was time resolve diabetic ketoacidosis (as defined by the study authors of the original articles). During the PROSPERO registration, the planned

secondary outcomes were the following: changes of biochemical markers in specified time intervals (pH, bicarbonate, base excess, level of chloride and potassium, and ketones), duration of insulin infusion, amount of total fluid administration, mortality, length of hospital stay (ICU), total), hospital or ICU readmission rate, change of renal function and the level of inflammatory biomarkers, and change in mental status. During the detailed analysis of the studies, we saw that the amount of total insulin administration and potassium levels as endpoints were included in several cases. Therefore, we chose to systematically collect data on these outcomes, which were not planned in advance in the protocol. However, due to the small number of studies we could only analyse the potassium levels. Regarding the biochemical markers, if there was more than one time point reported, we included the longest follow-up time reported, and we evaluated not only the absolute level of markers itself but also the delta value (change from baseline to the end of resuscitation level).

7.2.3 Data extraction, risk of bias, and quality assessment

Four authors (G.S., A.F., C.S., and C.T.) separately worked on data extraction from the included articles using a standardized form; also, an analyser programme and visual inspection were used to extract data from the graphs. We collected the following data: study characteristics, first author, country of origin, sample size, age, and gender data; and all the published outcomes relevant to our meta-analysis. After that, two authors (G.S. and C.T.) independently assessed the risk of bias. In the case of randomized controlled trials, the Revised Cochrane Risk of Bias Tool for randomized trials (RoB 2) was used; in the case of observational studies, the Risk Of Bias In Nonrandomized Studies – of Interventions (ROBINS-I) was applied (55, 56). The criteria to appraise the RCTs included the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported result, and overall bias. Any discrepancies between the authors were resolved by a third expert (A.M.).

The first author (G.S.) appraised the certainty of the evidence for this meta-analysis using the GRADE system and provided the Jadad score for the methodological quality of clinical trials (57, 67).

7.2.4 Statistical analysis

In the case of continuous outcomes, the median difference (MeD) with 95% CI was calculated as the effect size. The extracted values to estimate the MeD and its variance were the sample size, the median, and the lower and upper quartiles of the two groups, where available. To estimate the median and its variance in studies reporting mean and standard deviation, the distribution was assumed to be normal. The sampling variance of the medians was estimated using the QE method (68), and the random-effects model was used to summarise the MeDs. When the mean difference was calculated, it was also considered an effect measure with a 95% CI. Where the mean and standard deviation were not provided, the mean was estimated using the Luo method (60), and the standard deviation was estimated using the Shi method (61) based on the median and quartiles or minimum and maximum values. For the MD, the confidence intervals for individual studies were based on t-distribution.

To estimate the between-study variance τ^2 and its square root τ, the Restricted maximum-likelihood estimator (69) was used. To estimate the confidence interval of τ^2 and τ, the Q-Profile method (70) was used.

The odds ratio with 95% CI was used as the effect measure for binary outcomes. To calculate the OR, the total number of patients in each group and those with the event of interest was extracted from each study. Raw data from selected studies were pooled using a random-effects model. The Mantel-Haenszel method (71, 72) was used to handle only zero-cell counts for the pooled results. For studies with a zero-cell count, 0.5 was added to all cell frequencies for the odds ratio.

To estimate the between-study variance τ^2 and its square root τ, we used the Paule-Mandel estimator (73) and the Q-Profile method (70) for their confidence intervals.

Forest plots were used to summarise the results graphically. For all outcomes, statistical significance was defined as *p*-value <0.05.

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8. RESULTS

8.1 Study I.

8.1.1 Search and study selection

Based on PRISMA recommendations, the details of the electronic search are depicted in Fig. 1.

Our systematic search yielded 11,627 records and 3 other articles were found from other searches. After removing duplicates, 8695 items were screened, 32 of these were thought to be suitable for full text selection and finally 13 studies (7 RCTs (74-80) and 6 observational studies (81-86) were processed for data collection. One additional RCT was found during an internet search which was not in the aforementioned databases (87). Altogether 5393 patients' data were gathered in this review, 2574 of them were female (47.7%). Cohen's kappa for abstracts and full texts was 0.67 and 0.59, respectively. The characteristics of the studies included in our systematic review and metaanalysis are presented in Table 1.

DOI:10.14753/SE.2025.3197

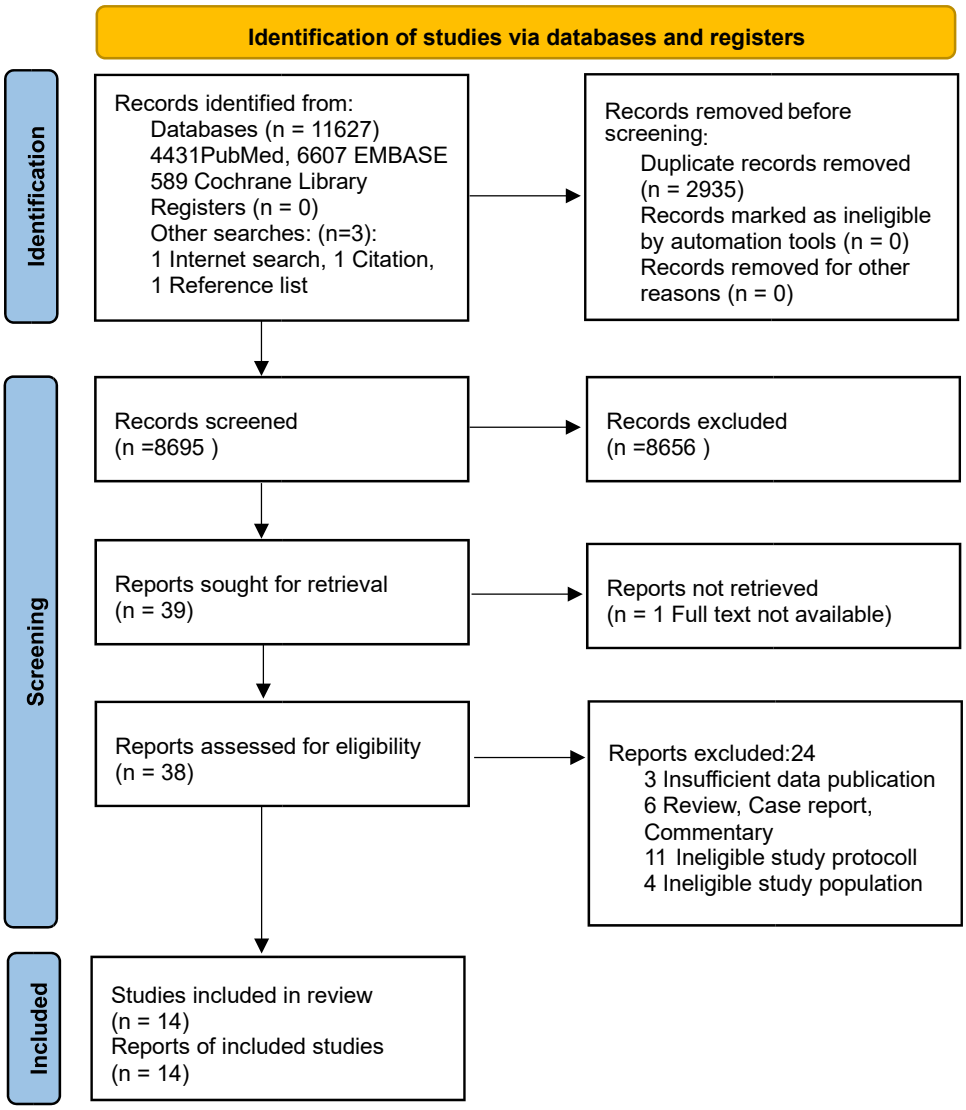

Figure 1: PRISMA flowchart

DOI:10.14753/SE.2025.3197

Table 1: Characteristic of included studies

Source	Study design (RCT /OBS)	Sample size (% male)	Examiner experience with PoCUS [a]	Examination protocol		Eligibility criteria [b;c]	Outcomes
				PoCUS	control		
Baker, 2020	RCT	442 (58)	mixed	Volpicelli's 8 view, subcostal cardiac clip (posterior lung not tested)	medical history, physical examination, ECG, blood test, CXR, echocardiography, CT	Inc: ≥60 years, able to understand and sign a written consent, not requiring immediate resuscitation Exc: no data	length of stay, mortality
Blans, 2021	OBS	61 [d] (52)	beginner	BLUE, cardiac: standard transthoracic windows: LV/RV dilatation and function, pericardial tamponade / effusion, subcostal view: IVC	not stated	Inc: call for MET based on Modified Early Warning Score Exc: pregnancy, requiring direct lifesaving intervention, GCS <9 or GCS declined ≥2 as the primary reason for MET attendance	mortality
Colclough, 2017	RCT	40 (55)	not specified	cardiac (based on Preoperative Pocket Echocardiography Trial)	not stated	Inc: National Health Service triage category 1–3 Exc: no data	time to diagnosis, mortality
Corsini, 2019	OBS	124 (61)	beginner	bilateral anterior, lateral, and posterior lung ultrasound,	CXR	Inc: ≥23 week of gestational age, RR >60, oxygen	time to diagnosis

				transabdominal scanning for lung bases and subcostal for diaphragm		supplementation, respiratory support Exc: CPR	
Harel, 2018	OBS	202 (61)	not specified	no data	CXR	Inc: <18 years, suspected pneumonia Exc: ED left before discharge, both PoCUS and CXR were made, PoCUS undertaken not by patient's treating physician	length of stay, readmission rate
Laursen, 2014	RCT	315 (43)	expert	FATE protocol, modified Volpicelli's 8 view, deep veins according to American College of Emergency Medicine's criteria	blood samples, blood gases, ECG, CXR, CT, echocardiography	Inc: RR >20, SAT <95%, coughing, chest pain Exc: permanent mental disability, PoCUS not done within 1 hour after the primary assessment	length of stay, readmission rate, mortality
Nakao, 2020	OBS	324 (49)	not specified	Volpicelli's 8 view	not stated	Inc: ≥50 years, suspected acute heart failure or COPD exacerbation Exc: ST-elevation myocardial infarction, known interstitial fibrosis, lobectomy or PTX	time to treatment, length of stay

Pivetta, 2019	RCT	518 (53)	not specified	Volpicelli's 8 view	past medical history, history of present illness, physical examination, arterial blood gas analysis, ECG, CXR, N-terminal pro-brain natriuretic peptide	Inc: sudden onset of dyspnea or increase in the severity of chronic dyspnea in the previous 48 hours Exc: mechanically ventilated at the time of first evaluation, dyspnea in context of trauma	time to diagnosis, length of stay, mortality
Riishede, 2021	RCT	211 (51)	expert	Volpicelli's 8 view (modified), subcostal or apical cardiac (4-chamber: pericardial effusion, LV function, RV overload)	clinical examination, blood samples, ECG, CXR, CT, echocardiography	Inc: coughing, chest pain, RR >20, SAT <95% Exc: PoCUS already done, inability to randomize or do PoCUS <4h	appropriate treatment, readmission rate, mortality
Seyedhosseini, 2017	RCT	50 (58)	mixed	BLUE protocol	patients' history, physical examination, CXR, biochemistry, CT	Inc: >12 years, Acute Respiratory Distress Syndrome within the past 7 days Exc: dyspnea due to previously diagnosed medical condition, need CPR on arrival	time to treatment, length of stay, mortality
Wang, 2014	RCT	128 (51)	expert	BLUE protocol, parasternal long-axis view to assess cardiac contractility and left ventricular ejection fraction,	bedside CXR, central venous and arterial blood gas parameters, myocardial injury marker levels, pulse	Inc: admitted to ICU with acute pulmonary edema, dyspnea in 48 hours, partial arterial oxygen pressure / fraction of inspired	time to diagnosis, length of stay, mortality

				subxiphoid view to assess IVC	index contour continuous cardiac output catheter, pulmonary artery catheter	oxygen <300 mmHg, bedside CXR showing ≥1 new sign of acute pulmonary edema according to the assessment of the attending ICU physician Exc: history of chronic cardiac dysfunction	
Wang, 2015	RCT	130 (49)	expert	extended FATE and BLUE-plus protocols were modified into a critical care ultrasonic examination protocol	vital signs, medical history, physical examination, laboratory tests, CXR, CT	Inc: required emergent critical consultation for pulmonary or circulation failures from medical / surgical units, post-surgical patients Exc: refused ICU transfer, already experienced cardiac arrest, advanced cancer	time to diagnosis, time to treatment, mortality
Zanobetti, 2017	OBS	2683 (51)	expert	LUS (longitudinal and oblique scans on anterolateral and posterior thoracic areas, according to Volpicelli), cardiac (apical 4-chamber view to evaluate left ventricular ejection fraction or presence of right ventricular	vital signs, medical history, physical examination, ECG, CXR, CT, echocardiography, blood sampling or arterial blood gas	Inc: acute dyspnea of every degree Exc: traumatic origin, discharged after ED evaluation	time to diagnosis

				dilatation, subcostal long axis to assess pericardial effusion and left ventricular ejection fraction), IVC			
Zieleskiewicz, 2021	OBS	165 (62)	mixed	cardiac (left and right ventricular function, pulmonary assessment), BLUE protocol, imaging of the deep veins when deemed necessary	taking medical history, performance of a circulatory, respiratory and neurological assessment, vital signs, blood testing, conduction of any additional tests judged necessary by the physician	Inc: medical or surgical wards and developing respiratory and/or circulatory failure justifying placement of a call to the RRT Exc: pregnancy, cardiac arrest, technical limitations to the performance of US, lung or cardiac transplant, RRT call for a neurological failure, RRT call by the ED and impossible follow-up	time to diagnosis, time to treatment, length of stay, appropriate treatment, mortality

Abbreviations: BLUE, Bedside Lung Ultrasound in Emergency; CPR, cardiopulmonary resuscitation; Exc, exclusion; FATE, Focus Assessed Transthoracic Echocardiography; GCS, Glasgow Coma Scale; Inc, inclusion; IVC, inferior vena cava (diameter); LUS, lung ultrasound; LV, left ventricule; MET, Medical

a) **Examiner practice: beginner: trained in basic level and/or low clinical experience; expert: trained in high level and/or high level of clinical experience.**

b) **Consent and dyspnea as an eligibility criteria is not specifically mentioned, due to being omnipresent.**

c) **Age restriction is highlighted only when children or older population were included.**

Emergency Team; OBS, observational study; RCT, Randomized Controll Trial; RR, respiratory rate/min; RRT, rapid response team; RV, right ventricule; SAT, peripherial oxygen saturation	d) **We received data from the authors just about patients treated with respiratory failure.**

8.1.2 Primary outcomes

Time to diagnosis was the most cited endpoint in the studies (7 of 15). PoCUS use compared to controls resulted in a significant reduction in time to making the diagnosis (MD − 63 min; 95% CI − 115 to − 11 min) (Fig. 2A). Time to treatment was reported in four studies. In the PoCUS group, patients also received treatment significantly earlier (MD − 27 min; 95% CI − 43 to − 11 min) compared to controls (Fig. 2B). Heterogeneity among these trials for both outcomes was considerable ($I2$ = 100%, p = 0 and 88%, p < 0.01, respectively).

As far as in-hospital LOS is concerned, PoCUS use showed no significant effect (MD − 0.02 days; 95% CI − 0.43 to 0.39 days), with low heterogeneity ($I2$ = 0%, p = 0.81). Regarding LOS in the ED, there was a mean of 35 min less waiting time to discharge or admission to a ward that proved not significant (MD − 35 min; 95% CI − 93 to 23 min), but heterogeneity was high ($I2$ = 84%, p < 0.01). Patients in the PoCUS group stayed for a significantly shorter time in the ICU than controls (MD − 1.27 days; 95% CI − 1.94 to − 0.61 days) (Fig. 2C). Heterogeneity was moderate among these trials ($I2$ = 46%, p = 0.16).

Figure 2A. Time to diagnosis (minutes)

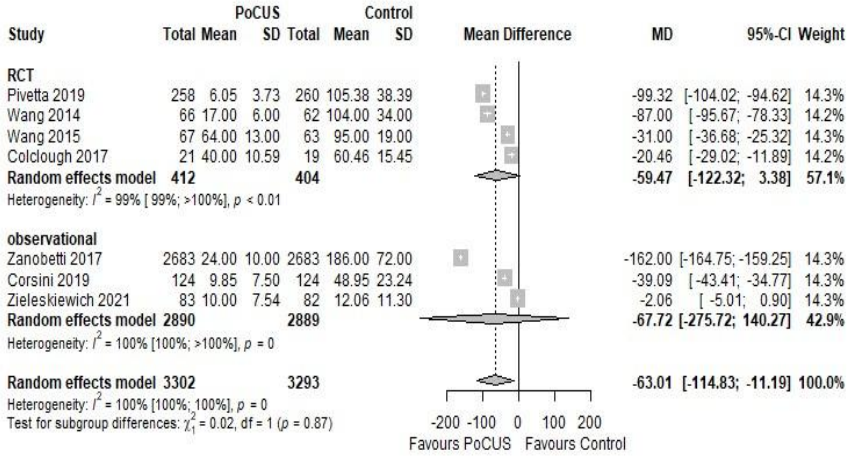

Figure 2B. Time to treatment (minutes)

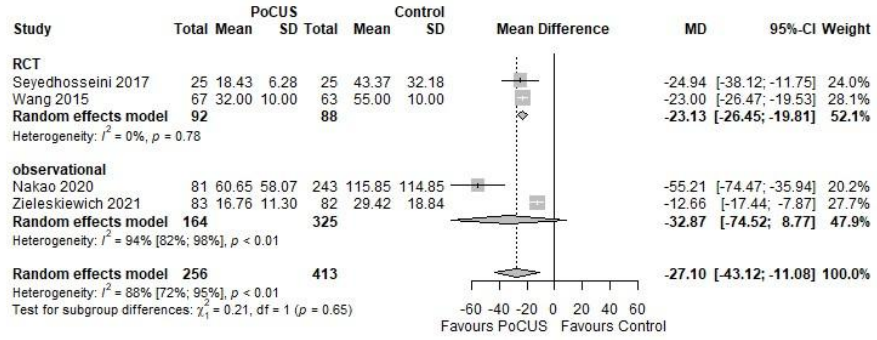

Figure 2C. Length of stay in the Intensive Care Unit (day)

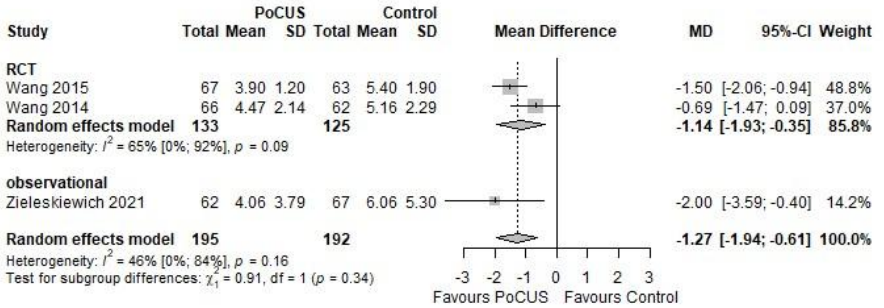

Figure 2. Primary outcomes in patients admitted with acute onset dyspnea when PoCUS was used compared to conventional modalities (control)

Comparison of patients admitted with dyspnea examined by PoCUS vs conventional modalities in time to diagnosis (considerable heterogeneity detected) (A), time to treatment (considerable heterogeneity detected) (B), and length of stay in the Intesive Care Unit (moderate heterogeneity detected) (C). PoCUS indicates Point of Care

Ultrasound; SD, standard deviation; MD, mean difference. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

8.1.3 Secondary outcomes

Regarding secondary endpoints, patients in the PoCUS group had significantly higher odds (OR 2.31; 95% CI 1.61 to 3.32) of receiving appropriate therapy compared to controls, and studies showed low heterogeneity ($I2$ = 0%, p = 0.67) (Fig. 3A).

We found no significant effects on 30-day re-admission rate (OR, 0.81; 95% CI, 0.56 to 1.17) with low heterogeneity ($I2$ = 0%, p = 0.78); 30-day mortality (OR, 0.82; 95% CI 0.31 to 2.18) and in-hospital mortality (OR 0.62; 95% CI 0.37 to 1.04), with moderate heterogeneity ($I2$ = 50%, p = 0.11 and $I2$ = 37%, p = 0.16, respectively) (Fig. 3 and the original publication's Additional Fig. 1). However, in the latter outcome, one article [Laursen (75)] appeared to be a potential outlier, but due to the low number of studies, the leave-one-out-analysis was discussed only in the original publication's Additional file (for more details see Additional Fig. 1).

Figure 3A. Rate of appropriate treatment

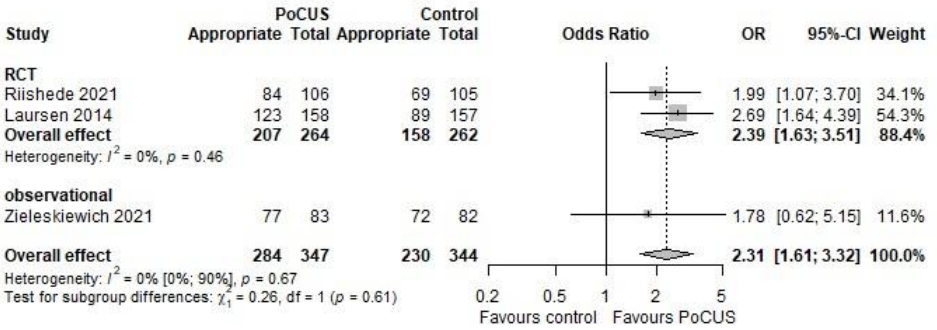

Figure 3B. 30-day readmission rate

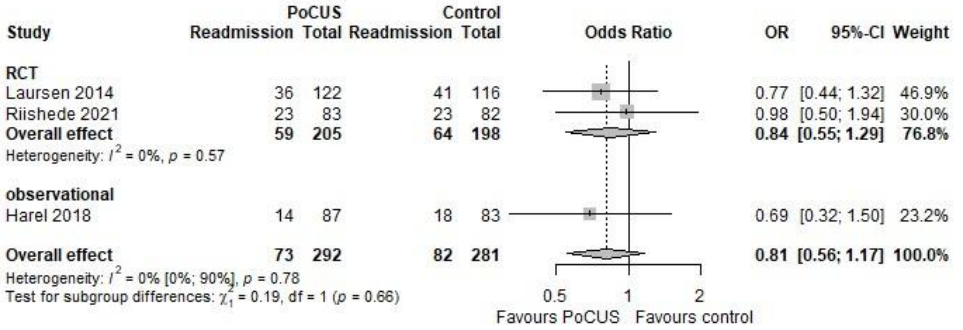

Figure 3C. Inhospital mortality

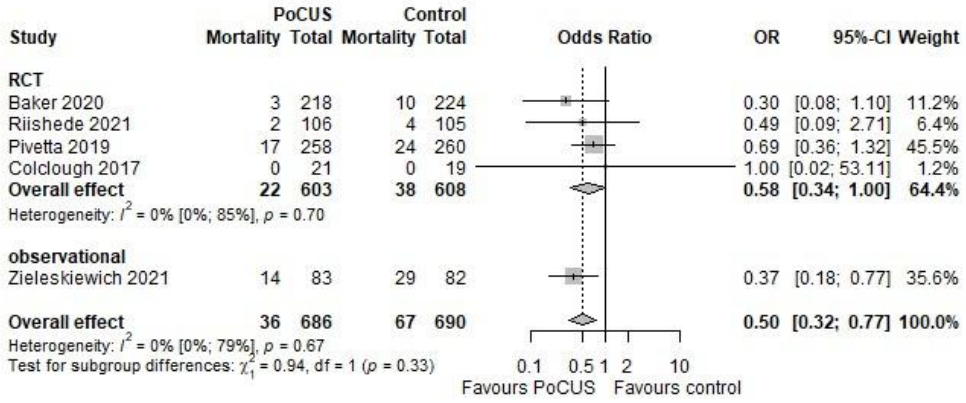

Figure 3. Secondary outcomes in patients admitted with dyspnea when PoCUS was used compared to conventional modalities (control)

Comparison of patients admitted with dyspnea examined by PoCUS vs conventional modalities in rate of appropriate treatment (low heterogeneity detected) (A), 30-day readmission rate (low heterogeneity detected) (B), and inhospital mortality (moderate heterogeneity detected) (C). PoCUS indicates Point of Care Ultrasound; OR, odds

ratio. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

8.1.4 Risk of bias assessment, publication bias and certainty of evidence

Based on the Cochrane proposal, the risk of bias assessment showed serious concern for only one article (84) and moderate (some concern in cases of RCTs) or low risk for all others. For GRADE, the certainty of evidence in the studies was variable, only the rate of appropriate treatment fell into high certainty category. The results of the risk of bias assessment of individual studies, the Funnel plots and the leave-one-out sensitivity analyses are shown in the original publication's Additional Files (Additional Tables 2, 3 and Additional Figs. 2, 3). Furthermore, the final GRADE assessment is also shown in in the original publication's Additional Table 1.

8.2 Study II.

8.2.1 Search and study selection

The literature search yielded a total of 7096 articles, and two other articles were found from other sources: one from Google Scholar and one from manual web search (17, 53) After duplicate removal, 5345 studies were left for the title and abstract selection; in the next step, 37 studies were found potentially useful for full-text selection, and 29 of them were assessed for eligibility; ultimately, ten records were considered for data extraction in our meta-analysis (17, 53, 88-95). Our study selection and screening process, along with our reasons for exclusion, are depicted in the PRISMA flow diagram (Figure 4). Eventually, seven randomized controlled trials and three observational studies were deemed eligible for inclusion in the meta-analysis. We contacted eight authors for data clarification or extra information on the outcomes; five authors responded (17, 88, 91, 92, 95).

During selection, we found trial protocols for two further ongoing trials. The first, encompassing 52 patients, listed the anticipated completion date as 2022. However, no results have been published yet (96). The second ongoing study started in 2009, and although no follow-up information was published, it has likely been discontinued (97).

The total number of patients included in our systematic review and meta-analysis was 1006, with 472 receiving BES and 534 treated with 0.9% saline. Generally, the included papers' sample sizes varied, ranging from 23 to 326. The characteristics of the evaluated studies are detailed in Table 2, and information about the included patients is described in the original publication's Supplementary material (Additional File 10.).

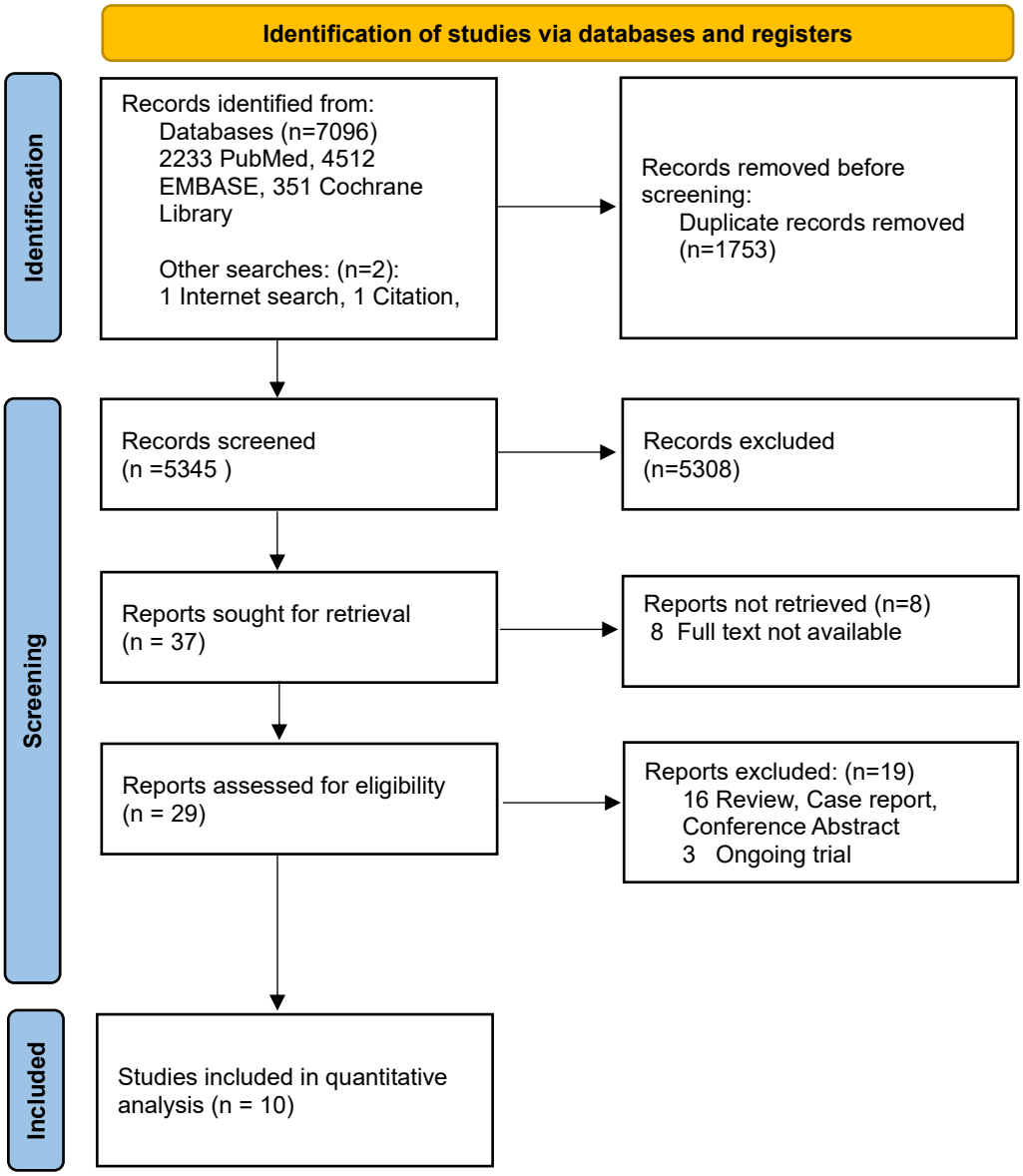

Figure 4: PRISMA flowchart

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Table 2: Characteristic of included studies

Source	Country, Study design (RCT/Obs)	Sample size (% male)	Inclusion criteria	Exclusion criteria	Type of BES	DKA resolution definition
Aditianingsih et al., 2017	Indonesia (RCT)	30 (37)	18-65y, accepted inclusion, glu[a] > 13.9 mmol/L, art pH < 7.35, positive blood ketone bodies	respiratory failure requiring mechanical ventilation, ESKD on hemodialysis, congestive heart failure, corrected Na >158 or <120 mmol/l, myocardial infarction with signs of heart failure, traumatic brain injury with cerebral edema signs, liver failure	Ringerfundin	Not detalied in the article
Carrillo et al., 2022	USA (Obs)	326 (57)	≥18y, admitted with DKA as a primary diagnosis	ESKD on dialysis, admitted from an outside facility, had been included in this study within the previous 30 days, were not initially treated with intravenous insulin, had a primary admission diagnosis other than DKA, receipt of similar amounts (<1 L difference) of RL and Saline, received no RL or Saline, pregnant, incarcerated	RL	AG < 14, se bicarb > 14 mmol/L, receiving enteral nutrition
Chua et al., 2021	Australia (Obs)	23 (52)	≥16y, moderate/severe DKA based on art pH < 7.24, predominant infusion PL or Saline for the initial 12 hours	> 500 ml of alternative crystalloids during the 12h study period; > 50 mEq of Na-bicarb and/or K-acetate as alkali therapy in the study period, ESKD or advanced chronic kidney disease with baseline estimated glomerular filtration rate < 30 ml/min/1.73 m^2	PL	Not detalied in the article
Mahler et al., 2010	USA (RCT)	45 (52)	18-65y, moder/severe DKA: glu>11.1	HHS, hyperglycemia without signs of DKA, mild DKA, > 500 ml of crystalloid or an insulin bolus before enrollment,	PL	AG ≤ 12

			mmol/L, bicarb ≤ 15mmol/l, AG ≥ 16	myocardial infarction, sepsis, respiratory failure, cerebral edema		
Oliver et al., 2018	USA (Obs)	84 (48)	18-89y, AG >10; pla glu > 13.9 mmol/L and ketonemia and/or ketonuria	received equal amounts of the 2 study fluids or > 1 L of the other study fluid from their assigned group	PL	blood glu < 11.1 mmol/L and 2 of the following: se bicarb ≥15 mEq/L, ven pH >7.3, and calculated AG ≤12 mEq/L
Ramanan et al., 2021	Australia (RCT)	90 (44)	≥16y, severe DKA: art pH ≤ 7.25 or se bicarb ≤ 15 mmol/L and glu ≥ 14 mmol/L and requirement for ICU admission in the judgement of the treating clinician	<16y, had previously been included in this trial, had a contraindication to either fluid or had a suspected diagnosis of the HHS	PL	pla glu < 11.1 mmol/L and two of the following: pla bicarb ≥ 15 mmol/L, ven pH > 7.3 and AG ≤ 12 mEq/L.
Rossman et l., 2017	Malaysia (RCT)	18 (56)	cap glu > 11 mmol/L, cap ketones > 3 mmol/L or urine ketones 2+ and ven pH < 7.3 and/or bicarb < 15 mmol/L	<18y, who were administered more than 500 ml other intravenous fluids or 50 ml of Na-bicarb within 24 hours, complicated with congestive heart failure or ESKD	Sterofundin	ketones < 0.3 mmol/L, ven pH > 7.3
Sardar et al., 2022	Pakistan (RCT)	164 (50)	20-60 years having pla glucose level less[b] than 13.9 mmol/L, art pH < 7.3, se bicarb < 15 mmol/L	Na > 150 mmol/L, K > 6.2 mmol/L, Cl > 113 mmol/L, patients with multiple co-morbidities e.g. stroke and ischemic heart diseases and extremely critical ill state	RL	se bicarb > 18 mEq/l

Self et al., 2020	USA (RCT)	172 (48)	>18y, included SALT-ED or SMART trial, DKA diagnosis at the present of ED evaluation rather than delayed onset of DKA after admission, pla glu > 13.9 mmol/L, pla bicarb ≤ 18 mEq/L, , AG >10 mEq/L	transfer from an outside hospital to the study ED, admission to the cardiac or neurologic ICU, presentation to the ED within 24 hours prior to a planned crossover in the trial	RL, PL	pla glu < 11.1 mmol/L and two of the following: pla bicarb ≥15 mmol/L, ven pH >7.3 and AG ≤12 mmol/L
Van Zyl et al., 2011	South Africa (RCT)	54 (57)	>18y, known or newly diagnosed type 1 or type 2 DM, ven pH 6.9–7.2, ≥ 2+ ketones on urine dipstick test, cap glu > 13 mmol/L and able to give verbal informed consent	another cause for acidosis was present, e.g. ESKD or lactic acidosis, if severely ill and in need of inotropic or ventilatory support, > 1 L of resuscitation fluid was administered before enrolment	RL	ven pH > 7.3, se bica ≥ 18 mmol/l and blood glu < 11.1 mmol/L

Abbreviations: RCT: Randomized Controlled Trials, Obs: observational studies, BES: balanced electrolyte solutions, DKA: diabetic ketoacidosis, y: years, glu: glucose, art: arterial, ESKD: end stage kidney disease, RL: Ringer's lactate, AG: anion gap, se: serum, bicarb: bicarbonate, PL: Plasma-Lyte, HHS: hyperosmotic hyperglycemic non-ketotic syndrome, pla: plasma, ICU: intensive care unit, cap: capillary, ED: emergency department, DM: diabetes mellitus.

[a] Where the source of the concentration (serum or plasma) was not indicated, the article did not provide details.

[b] We assume it was a typo; we send an email to the corresponding author but no answer has arrived.

8.2.2 Primary outcome

Three randomized studies, with a total of 316 patients, reported time to DKA resolution (92, 94, 95). The difference in means between the intervention and control arms was significant (MD: −5.36 [CI −10.46, −0.26] hours; I2, 54%) (Figure 5). Only one observational study evaluated this endpoint, so it was not possible to compare it with other non-randomized articles (91).

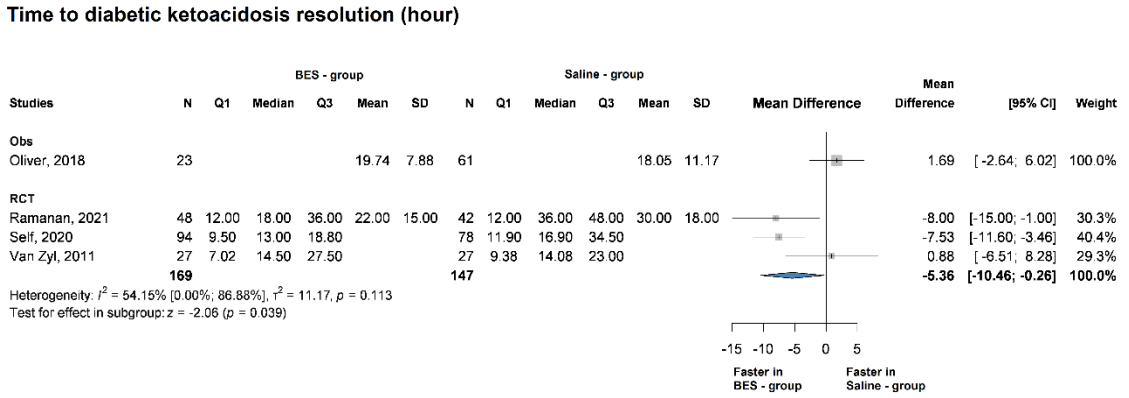

Figure 5. Primary outcome. Time to diabetic katoacidosis resolution

Comparison of patients admitted with diabetic ketoacidosis treated with Balanced Electrolyte Solutions (BES – group) versus 0.9% Saline (Saline – group). SD: standard deviation, Obs: observational study, RCT: Randomized Controlled Trials, CI: 95% Confidence Intervals. Mean Difference measured in hours. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

8.2.3 Secondary outcomes

Post-resuscitation electrolyte and bicarbonate levels are depicted in Figure 6. Four studies reported on chloride levels, which were significantly lower (MD: −4.26 [CI −6.97, −1.54] mmoL/L; *I*2 95%) in the BES – group (Figure 6A; 53, 90, 92, 94) similarly to serum sodium levels (MD: −1.38 [CI −2.14, −0.62] mmoL/L; *I*2 0%) (Figure 6B). Potassium was numerically higher in the BES – group compared to the Saline – group (MD: 0.18 [CI −0.16, 0.53] mmoL/L; *I*2 95%), but this difference did not reach statistical

significance (Figure 6C). Bicarbonate was significantly elevated in the BES – group (MD: 1.82 [CI 0.75, 2.89] mmoL/L; *I*2 1%) (Figure 6D).

There was no statistically significant difference between the groups regarding the duration of parenteral insulin administration (MD: 0.16 [CI −3.03, 3.35] hours; *I*2 0%) (Figure 7A); however, only three observational studies reported this outcome (17, 89, 91). We found three randomized and three observational studies reporting data about the amount of total fluid administration, but there were no significant differences between the two groups in any of the cohorts (observational studies MD: 181 [CI −173, 536] mL; *I*2 32%; and randomized studies MD: 86 [CI −584, 756] mL; *I*2 0%) (Figure 7B) (17, 89, 91 and 88, 92, 94).

With regard to the dichotomous variables of randomized trials, there was no difference in hyperkalaemia between the groups (OR: 1.07 [CI 0.21, 5.32]; *I*2 58%) (Figure 8A). Although the point estimate for hypoglycaemic episodes indicated more frequent episodes in the Saline – group, this difference was not statistically significant (OR: 0.55 [CI 0.22, 1.38]; *I*2 0%) (Figure 8B). Mortality was an extremely rare event in both the observational study and in the RCTs, with a total of 6 deaths out of 321 in the BES – group and 11 out of 339 in the Saline – group. For this reason, we publish the forest plot of this outcome only in the original publication's Supplementary material (Additional File 1.) (17, 92-95).

Due to less than three studies reporting on the following outcomes: change in the level of chloride and bicarbonate from baseline to the end of resuscitation, the amount of total insulin administration, in-hospital LOS, and LOS in the ICU, it was not possible to evaluate these outcomes in the meta-analysis. Nevertheless, these results are summarised in the original publication's Supplementary material (Additional File 1.). Finally, all outcomes that were registered in advance in PROSPERO but were not poolable are listed in the original publication's Supplementary material (Additional File 5.).

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Figure 6A. Post-resuscitation chloride levels (mmol//L)

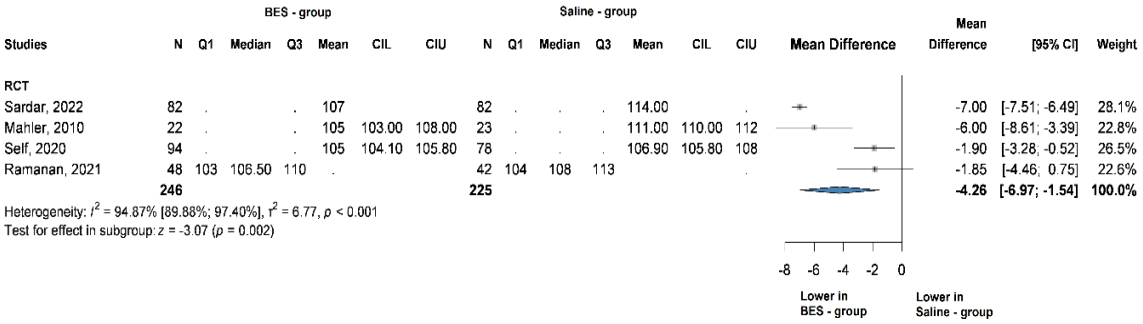

Figure 6B. Post-resuscitation sodium levels (mmol//L)

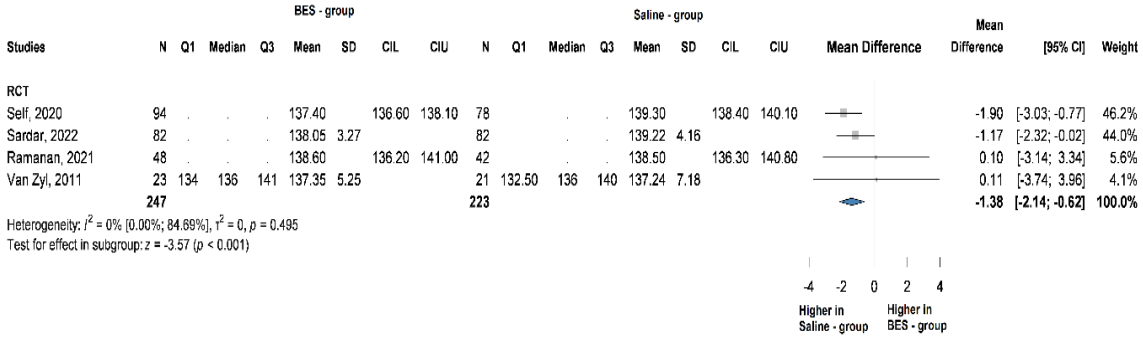

Figure 6C. Post-resuscitation potassium levels (mmol//L)

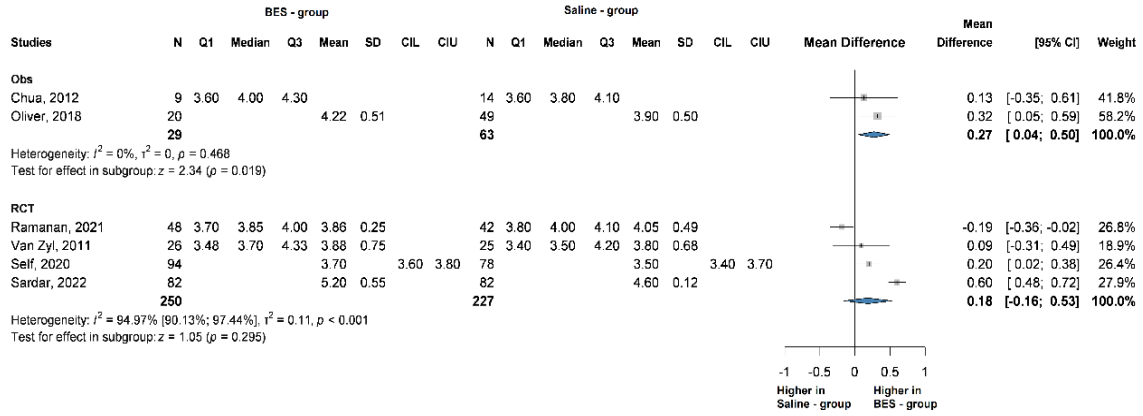

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Figure 6D. Post-resuscitation bicarbonate levels (mmol//L)

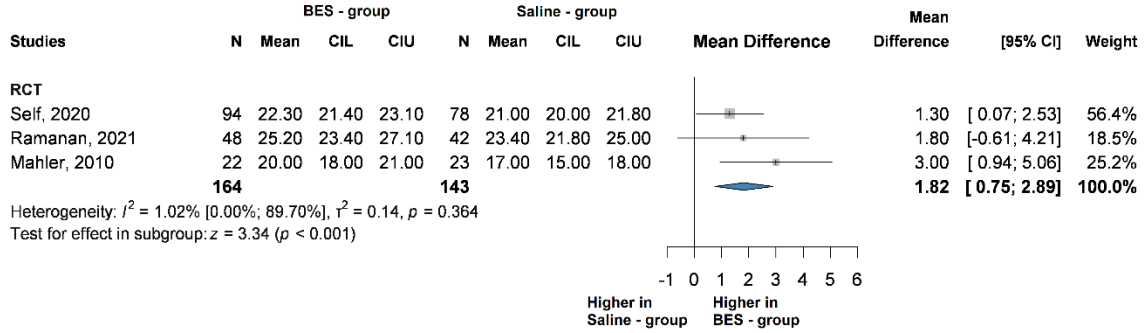

Figure 6. Secondary outcomes. Post-resuscitation electrolyte and bicarbonate levels

Comparison of patients admitted with diabetic ketoacidosis treated with Balanced Electrolyte Solutions (BES – group) versus 0.9% Saline (Saline – group). SD: standard deviation, CIL and CIU: Confidence Intervals Lower and Upper, Obs: observational studies, RCT: Randomized Controlled Trials, CI: 95% Confidence Intervals. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

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Figure 7A. Duration of parenteral insulin administration (hour)

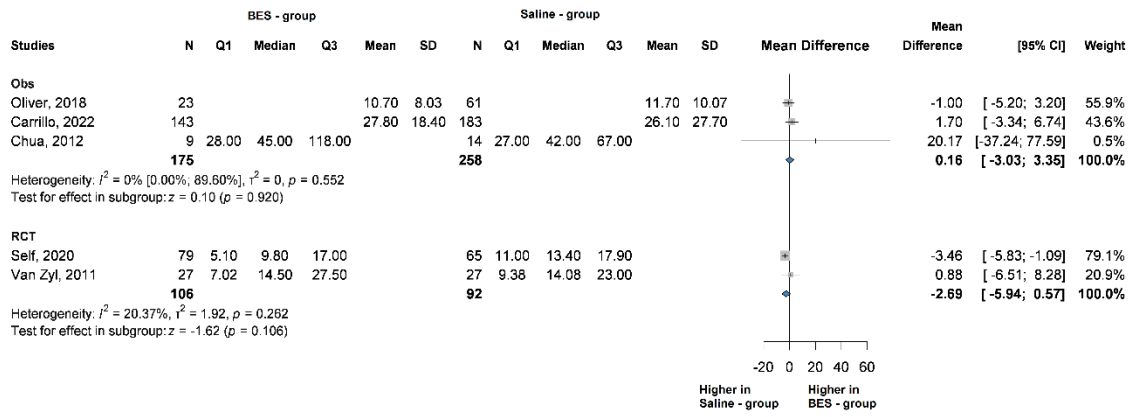

Figure 7B. Amount of total fluid administration (ml)

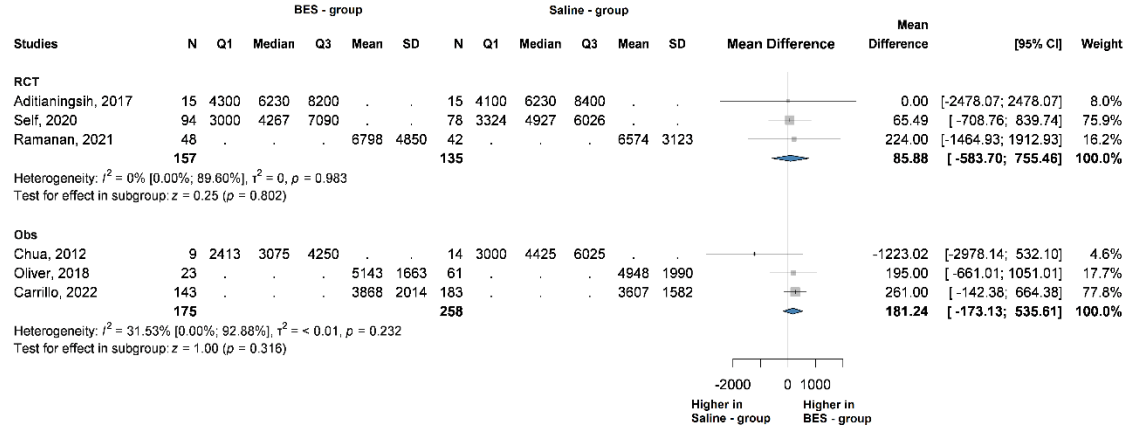

Figure 7. Secondary outcomes. The duration of parenteral insulin administration and the amount of total fluid administration

Comparison of patients admitted with diabetic ketoacidosis treated with Balanced Electrolyte Solutions (BES – group) versus 0.9% Saline (Saline – group). SD: standard deviation, Obs: observational studies, RCT: Randomized Controlled Trials, CI: 95% Confidence Intervals. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.

Figure 8A. Hyperkalaemia

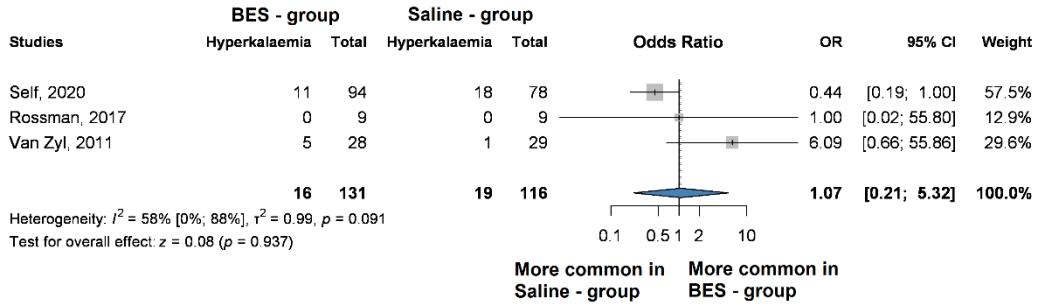

Figure 8B. Hypoglycaemia

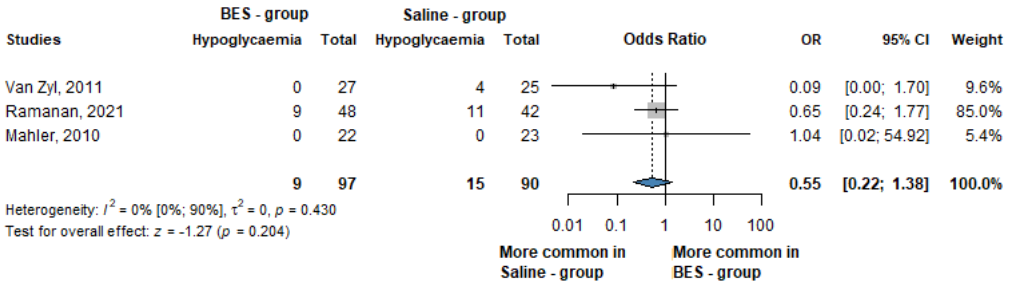

Figure 8. Secondary outcomes. Hyperkalaemia and hypoglycaemia

Comparison of patients admitted with diabetic ketoacidosis treated with Balanced Electrolyte Solutions (BES - group) versus 0.9% Saline (Saline – group). OR: Odds Ratios, CI: 95% Confidence Intervals. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI. All the studies are Randomized Controlled Trials

8.2.4 Risk of bias

Most of the randomized studies had low or some concerns of bias, but particularly, the study by Ramanan et al. was assigned a high risk of bias due to the randomisation method (92). Regarding the observational studies, all were considered at moderate risk of bias; only the study by Carrillo et al. showed a serious risk of bias (17). The detailed risk of bias assessment for RCTs and observational studies are listed in the original publication's Supplementary material (Additional Files 6-7.).

8.2.5 Quality assessment

The quality of evidence was low, as appraised by the GRADE criteria for the primary outcome of time to DKA resolution. Serious inconsistency and risk of bias were the main

reasons for the downgrading. Details about other outcomes and our quality assessment can be found in the original publication's Supplementary material (Additional File 8.). The Jadad score was lower than three points in four studies, the results of which are also published in the original publication's Supplementary material (Additional File 9.).

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9. DISCUSSION

9.1 Summary of findings, international comparisons

9.1.1 Study I.

The results of this systematic review and meta-analysis have shown that patients admitted with acute onset dyspnea and managed with PoCUS have a significantly shorter time to diagnosis, time to treatment, higher rate of receiving appropriate treatment, and decreased stay in ICU compared to conventional approaches. However, use of PoCUS has a limited influence on 30-day and in-hospital mortality and had no relevant effect on the 30-day re-admission rate.

Due to the fact that approximately 20% of patients presenting to the ED with dyspnea are misdiagnosed and consequently inappropriately treated (98), PoCUS could have a potential role as an important diagnostic tool in patient management (99). Our results provide high-level evidence to support this hypothesis. PoCUS has several advantages over conventional modalities, such as immediate availability of results (33), lack of ionizing radiation (38), costeffectiveness (100), reproducibility (11), independency of the patients' breath-holding capacity (11), portability and safety (101). Although PoCUS use has increased substantially in critical care settings over the last two decades (11, 102, 103), it still remains underused (36), as indicated by the lower than expected prevalence of PoCUS devices in rural areas (104) and its use in only around 5% of patients in the ED (105). This tendency can, in part, be explained by the lack of standardized training facilities (38), the operator dependency that hinders quality assurance (106), and most importantly the lack of high-quality evidence-based guidelines on PoCUS (101, 103, 107). Our results provide substantial evidence that PoCUS use should be promoted on both national and international levels, and measures should be taken to improve its implementation and practice.

Several reviews have investigated the diagnostic accuracy of PoCUS in patients with dyspnea (9, 10, 34, 35, 37, 41, 42, 106, 108), but only a couple have included similar outcomes to ours (36, 109).

Our results are in contrast with a recently published guideline (107), which states that clinicians may use PoCUS in addition to the standard diagnostic pathway when there is diagnostic uncertainty. Based on our results, we recommend that all patients suffering from acute onset dyspnea should be managed by PoCUS as a standard and not only as a supplementary tool when standard diagnostic measures fail.

Alrajab et al. (36) reported in a meta-analysis that the PoCUS group needed a significantly shorter time to show the presence or absence of pneumothorax. Their results are in line with our findings that PoCUS use can reduce time to diagnosis by more than one hour. A recent systematic review and meta-analysis that included 49 studies with data on 9782 participants found that PoCUS had no effect on in-hospital LOS (109), which is in accordance with our results. To the best of our knowledge, ED and ICU staying as separate outcomes have not been evaluated in previous meta-analyses. Hence, ours is the first to report on these. According to our results, PoCUS use may reduce LOS in ED and the ICU, which could have other potential beneficial effects (e.g., decreased costs and/or reduced emergency room wait times) that should be investigated in future.

Regarding 30-day re-admission rates, although there was a tendency in favor of PoCUS, similar to the American College of Physicians guideline (107), we could not demonstrate any statistically significant effect.

Garthlehner et al. (109) found no statistically significant differences for in-hospital mortality based on the analysis of three RCTs (75-77). Since this review, two further studies have been published (78, 86) that were included in our analysis, thereby we found a tendency toward PoCUS reducing in-hospital mortality, but it was not significant. Nevertheless, this positive signal in our study should encourage further research in the field.

In a prospective, comparative study by Silva et al. (110), PoCUS, compared to routine clinical assessment, significantly improved the rate of appropriate treatment in patients admitted to ICU with acute respiratory failure. However, it is important to note that this outcome was defined based on local treatment guidelines which may differ from center to center, and in one article (86) was not defined at all. In our analysis, we included patients from the ED as well as from medical and surgical wards. Our results from a broader perspective also suggest that the rate of appropriate treatment can definitely be improved using PoCUS.

9.1.2 Study II.

Considering that adequate fluid resuscitation is one of the cornerstones of the acute management of DKA, there are notably few high-quality articles available to date that are concerned with determining the optimal infusion. Meanwhile, despite its high sodium and chloride concentrations, 0.9% saline remains the most commonly used infusion solution, recommended by several guidelines (16, 17, 20-24).

There are few well-prepared studies reporting on our primary outcome. Nevertheless, guidelines recommend 0.9% Saline in general (GRADE B, Level 2) as initial fluid therapy in DKA while giving the clinicians the freedom to select BES as a first choice if they wish (21, 23); for Levels of Evidence and Grades of Recommendation see the original publication's Supplementary material Additional File 8.). In contrast, following the same framework for levels of evidence, BES could receive a level 1A recommendation in future guidelines due to the results of our meta-analysis (111).

Our review analysed ten articles from 6 countries, all comparing 0.9% saline to BES of different types.

Regarding time to DKA resolution Ramanan et al. and Self et al. found a tendency favouring BES (92, 94). In contrast, Van Zyl et al. found faster resolution using 0.9% Saline, but the sample size was relatively small, resulting in a wide confidence interval (Figure 2) (95). However, compared to the other studies, there were differences in patient baseline characteristics, inclusion criteria, diversity in DKA management protocols, and different definitions for DKA resolution (these differences are detailed in the original publication's Supplementary material Additional File 11.). These differences may account for the different outcomes in the aforementioned papers.

In a previous systematic review and meta-analysis, which included 8 RCTs (n = 482 patients) on this topic, Alghamadi et al. found a longer time to resolution of DKA in the Saline – group (MD: 3,51 [CI 0.9, 6.12] hours), which is in accord with our findings (19). However, this study included children, whereas our review question only investigated adult patients. Furthermore, their paper included an abstract (Tsui et al., 2019) that has not been peer-reviewed, and for this reason, it was excluded from our data set (112). Regarding postresuscitation serum chloride (MD: 1.62 [CI −0.40, 3.64] mmoL/L) and bicarbonate levels (MD: −1.50 [CI −2.33, −0.67] mmoL/L) in the Saline – group versus the BES – group, their results are very similar to our findings.

Another meta-analysis from Catahay et al. also found that the pooled hazard ratio for faster DKA resolution was 1.46 (CI 1.1, 1.94, p = 0.009) (52). However, the MD of −3.02 h (CI −6.78, 0.74) did not reach statistical significance, unlike in our study. The mean-median conversion could explain this difference. We were also able to assess additional outcomes, including post-resuscitation electrolyte and bicarbonate levels, duration of parenteral insulin administration, and the amount of total fluid administration.

BES and 0.9% saline solutions were compared in several other studies in other fields of critical care, with most of them finding no significant differences in the occurrence of AKI, the need for RRT, hospital LOS, and mortality (43, 44, 46, 50, 51, 113). In contrast, Hammond et al. found significant differences in AKI and mortality in favour of BES in a meta-analysis that included more than 30,000 critically ill patients' data (45). A key difference between that meta-analysis and our study was that they included unselected, critically ill patients. Furthermore, according to Yunos et al., a significant reduction in AKI and RRT was achieved when chloride-restrictive intravenous infusion was compared with liberal therapy (114). Lastly, Self et al. reported a significant reduction in major adverse kidney events in the BES arm compared to 0.9% saline in noncritically ill adults (49). Although we also intended to analyse the effects of BES versus 0.9% saline on renal function, LOS, and mortality, the included studies unfortunately did not provide enough high-quality data for these purposes. However, the higher post-resuscitation serum chloride and sodium levels in the Saline – group that we found in our study could be predisposing factors for AKI, as hyperchloraemia and hypernatraemia may be associated with decreased renal perfusion (26).

It is important to note that the studies included differed in the specific crystalloids used in the BES – group. These balanced solutions have different compositions and therefore may have different clinical effects (115). Excessive administration of balanced solutions may result in hyperlactatemia, metabolic alkalosis, hypotonicity (with compounded sodium lactate), and cardiotoxicity (with acetate) (116). It is also well-known that balanced solutions using organic anions (e.g., lactate, acetate, gluconate, pyruvate, or malate) could influence the strong ion difference, possibly affecting the plasma pH.

As the evaluated articles in our study were published in different countries, there may be differences in endpoint measurements and follow-up. The blood glucose measurement reported by Van Zyl et al. was measured from a capillary sample, which may not always give an accurate result (95). In the study conducted by Rossman et al., the length of follow-up was only 12 h due to logistic considerations and financial constraints,

consequently there was not enough time for complete resolution of acidosis and ketone clearance (93).

Furthermore, inclusion and exclusion criteria in the evaluated articles differed, for example, Self et al. included critically ill patients, whereas Sardar et al. and van Zyl et al. excluded this subgroup (48, 53, 94, 95). Aditianingsih et al. excluded patients requiring mechanical ventilation, and Mahler et al. excluded patients with respiratory failure, while in the study conducted by Ramanan et al., 19% of the subjects in the Saline – group required mechanical ventilation (88, 90, 92). These differences may partly explain the different levels of heterogeneity in the processed outcomes (Figuress 5-8 and original publication's Supplementary material Additional File 2.).

Differences in DKA severity could also impact the results, but these were only reported by Carrillo et al., Chua et al., and Self et al. (17, 89, 94). Nevertheless, APACHE II, APACHE III, and Elixhauser Comorbidity Index Scores did not show any differences between the BES and 0.9% Saline – groups in these studies.

9.2 Strengths

9.2.1 Study I.

To the best of our knowledge, this systematic review and meta-analysis on the use of PoCUS in patients with acute onset dyspnea is one of the largest and most comprehensive studies to date. The strengths are the application of a rigorously followed protocol prospectively registered on PROSPERO, the evaluation of the overall quality of evidence using the GRADE system, and being up to date by incorporating the most recent literature. We also included studies examining clinical outcomes, regardless of their language or publication date, not just those evaluating diagnostic accuracy. Additional strengths include the assessment of highly relevant clinical outcomes (99) and the fact that there were no relevant missing data in the included studies. In contrast to previous reviews and meta-analyses (33-37, 106) that analyzed data from patients with an explicit diagnosis, such as pneumonia or acute decompensated heart failure (9, 10, 33, 34, 108), we applied a broader definition of dyspnea, thereby including more patients and providing more comprehensive results.

In the case of one study (Blans), the author kindly provided the original data on patients with dyspnea, excluding all other causes (82). This allowed us to have a more homogeneous population and is the reason for the differences in patient numbers presented in their original article and in our analyses.

9.2.2 Study II.

To the best of our knowledge, the present study is the most up-todate and comprehensive meta-analysis on this topic. We followed a rigorous methodology in the systematic search and focused on a prespecified population in both the intervention and control arms. Unlike existing meta-analyses, we focused our review question on adult patients for optimal clinical decision-making utility. Furthermore, we analysed more endpoints than other reviews, focusing on all available important patient-centred outcomes. We also contacted the authors whenever there were discrepancies or questions regarding the results.

9.3 Limitations

9.3.1 Study I.

Our study also has certain limitations. There was substantial heterogeneity regarding the age groups as we included infants and patients older than 59 years (76, 83). Severity of illness, as indicated by the patients' different medical conditions, also showed heterogeneity as some articles included intubated, mechanically ventilated patients, while others excluded this group (77, 83). Furthermore, not all patients had dyspnea only as the sole complaint. Some articles also included patients with coughing or chest pain, which further increased the heterogeneity of the study population (Table 1). However, we tried to overcome this issue by including studies where the majority of subjects required medical intervention for acute onset dyspnea and included them in data collection and analysis. The diversity of PoCUS protocols may be another important factor behind the high heterogeneity of the results and this is a key point and limitation at the same time, from both the methodological and clinical points of view. For example, some studies used PoCUS only to investigate the lungs, whereas others examined the heart or both heart and lungs, while some studies also evaluated the venous system (Table 1). Furthermore, there

is a lack of standardization regarding PoCUS training and practice. Hence, we cannot exclude that in this regard there was substantial diversity in the included studies.

Additionally, there were also some challenges in the interpretation of the reported data. For example, extracting numerical data from figures was particularly difficult, and in one case (84) the re-admission rate period was 21 days instead of 30 days.

Regarding the outcomes, on the one hand, it should be noted that time to diagnosis could be influenced by the operator's experience. On the other hand, classification of the primary and secondary end points was arbitrarily defined by us at the time of the PROSPERO registration. This was followed throughout the analysis and not modified subsequently, although not all articles used exactly the same classification as we did.

Nevertheless, these limitations highlight the importance and need for the development of gold standards for the management of this patient population to improve quality of care.

9.3.2 Study II.

Our study has considerable limitations. First, the definition of 'DKA resolution' showed certain differences in the included studies (e.g., bicarbonate and anion gap cut-off values, see Table 2). Furthermore, the severity of DKA in the evaluated patients and the age restrictions set out in the inclusion criteria were also different. Sardar et al. included subjects aged between 20 and 60 years, while Rossman et al. set no upper age limit (53, 93). Another important limitation is that the treatment protocol for DKA varies from country to country, and the protocol itself was not always fixed in the studies, which may have led to differences, for example, some hospitals used bicarbonate to resolve DKA, while others limited its use (20-23).

The volume of fluid administered during resuscitation in DKA could also have a substantial impact on the outcomes. Unfortunately, this was only reported in six trials and may be a potential limitation of our study. There were no data available on the intensity of fluid resuscitation in the studies. Usually, they followed certain guidelines or local protocols, but the actual approach was not described in detail.

Although we were able to include ten articles in our analysis, only a small number of studies analysing the same outcome were available, which is also a major limitation. Finally, data extraction from, analysis of, and comparison between the articles was also a

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major challenge (e.g., Self et al. used smoothed data, and the data had to be read from curves) (94).

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10. CONCLUSION

10.1 Study I.

The results of this systematic review and meta-analysis support the use of PoCUS to improve differential diagnosis, achieve early appropriate treatment and decrease LOS in the ICU compared to conventional diagnostic modalities in patients admitted with acute onset dyspnea.

10.2 Study II.

Our systematic review and meta-analysis of the currently available data indicate that BES resolves DKA faster than 0.9% saline, although the level of evidence remains low, and more research on this topic should be encouraged. According to our results, DKA guidelines should consider BES instead of 0.9% saline as the first choice during fluid resuscitation. Furthermore, we found that resuscitation with BES results in lower serum sodium and chloride concentrations but higher bicarbonate concentrations after the DKA resolution compared to 0.9% saline; meanwhile, we acknowledge that the clinical importance of the observed differences is disputable.

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11. IMPLEMENTATION FOR PRACTICE

11.1 Study I.

The results of this systematic review and meta-analysis indicate that all patients admitted with acute onset dyspnea should be examined with PoCUS to reduce time to diagnosis, time to treatment, LOS and potentially mortality.

11.2 Study II.

Although further trials are still needed to reach the highest level of evidence, we still believe that the data currently available provide enough support to change the recommendations in DKA management guidelines and replace 0.9% saline with the more physiologically balanced electrolyte solutions as the first choice during fluid resuscitation in patients admitted with DKA (117, 118).

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12. IMPLEMENTATION FOR RESEARCH

12.1 Study I.

There are several positive signals in our results that should encourage further research in this field. To optimize PoCUS use in daily routine, further studies are needed in which patient selection criteria provide a more homogeneous population, and the experience of the examiners is also well defined. Finally, standardizing PoCUS protocols is of paramount importance and is a challenging task for the future.

12.2 Study II.

Although the data available so far seem very convincing that BES should be the first-line infusion in adult DKA fluid resuscitation, it is clear that further well-designed and carefully conducted randomised controll trials in large patient populations are needed. It is crucial that these use the same DKA resolution definition and similar therapeutic protocols, as only then can they be included in further analyses.

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13. IMPLEMENTATION FOR POLICYMAKERS

Policymakers have the opportunity and responsibility to optimize patient care at the management and logistical level. High-quality, well-designed, and executed examinations are essential for the flawless performance of these tasks, as they are the only way to obtain a credible picture of the problems to be solved and the therapeutic options. This is particularly true for pathologies requiring emergency care, whose heterogeneity and temporal variability require sound knowledge and proven interventions. The intervention options explored in this thesis meet these requirements, and it is hoped that decision-makers will be able to use them to take appropriate steps to improve existing guidelines and their implementation.

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14. FUTURE PERSPECTIVES

Diseases requiring acute intervention will always be with us, but their care - with the proper knowledge and tools - needs to be increasingly rapid, adequate, and patient-centered.

It is hoped that the present study will contribute to faster and more accurate diagnosis and earlier access to appropriate therapy for patients treated with dyspnea using PoCUS.

It would also be a step forward to improve fluid balance in adults hospitalised for DKA with the correct type of BES infusion, leading to faster DKA resolution and fewer unwanted ion imbalances.

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16. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

16.1 Publications related to the thesis

- Szabó, G.V., Szigetváry, C., Szabó, L. et al. Point-of-care ultrasound improves clinical outcomes in patients with acute onset dyspnea: a systematic review and meta-analysis. Intern Emerg Med 18, 639–653 (2023). https://doi.org/10.1007/s11739-022-03126-2 Q1 IF: 3.2
- Szabó GV, Szigetváry C, Turan C, et al. Fluid resuscitation with balanced electrolyte solutions results in faster resolution of diabetic ketoacidosis than with 0.9% saline in adults – A systematic review and meta-analysis. Diabetes Metab Res Rev. 2024;e3831. https://doi.org/10.1002/dmrr.3831 D1 IF: 4.6

16.2 Publications not related to the thesis

- Szigetváry, C.; Szabó, G.V.; Dembrovszky, F.; Ocskay, K.; Engh, M.A.; Turan, C.; Szabó, L.; Walter, A.; Kobeissi, F.; Terebessy, T.; et al. Individualised Positive End-Expiratory Pressure Settings Reduce the Incidence of Postoperative Pulmonary Complications: A Systematic Review and Meta-Analysis. J. Clin. Med. 2024, 13, 6776. https://doi.org/10.3390/jcm13226776 Q1 IF: 3.0

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