Inclusion and definition of acute renal dysfunction in critically ill patients in randomized controlled trials: a systematic review

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Abstract

Background: In evidence-based medicine, multicenter, prospective, randomized controlled trials (RCTs) are the gold standard for evaluating treatment benefits and ensuring the effectiveness of interventions. Patient-centered outcomes, such as mortality, are most often the preferred evaluated outcomes. While there is currently agreement on how to classify renal dysfunction in critically ill patients, the application frequency of this new classification system in RCTs has not previously been evaluated. In this study, we aim to assess the definition of renal dysfunction in multicenter RCTs involving critically ill patients that included mortality as a primary endpoint.

Methods: A comprehensive search was conducted for publications reporting multicenter randomized controlled trials (RCTs) involving adult patients in intensive care units (ICUs) that included mortality as a primary outcome. MEDLINE and PUBMED were queried for relevant articles in core clinical journals published between May 2004 and December 2017.

Results: Of 418 articles reviewed, 46 multicenter RCTs with a primary endpoint related to mortality were included. Thirty-six (78.3%) of the trial reports provided information on renal function in the participants. Only seven articles (15.2%) included mean or median serum creatinine levels, mean creatinine clearance or estimated glomerular filtration rates. Sequential organ failure assessment (SOFA) score was the most commonly used definition of renal dysfunction (20 studies; 43.5%). Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria were used in five (10.9%) trials. In thirteen trials (28.3%), no renal dysfunction criteria were reported. Only one trial excluded patients with renal dysfunction, and it used urinary output or need for renal replacement therapy (RRT) as criteria for this diagnosis.

Conclusion: The presence of renal dysfunction was included as a baseline patient characteristic in most RCTs. The RIFLE, AKIN and KDIGO classification systems were infrequently used; renal dysfunction was generally defined using the SOFA score.

Keywords: Acute kidney injury, Critically ill, Intensive care unit, Mortality, Systematic review

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Background
Acute renal dysfunction affects one in five hospitalized patients [1] and occurs in up to 25% of critically ill individuals [2, 3]. Renal dysfunction is an independent risk factor for mortality, especially in patients treated with renal replacement therapy (RRT) [4]. Recent epidemiological studies have shown that renal dysfunction is associated with prolonged hospital stay, increased hospitalization costs, and progression to chronic kidney disease [2, 5].

Since 2004, the severity of kidney injury has been determined by several new classification systems: Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE), Acute Kidney Injury (AKI) Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) [6]. These systems have provided a standardized assessment of renal dysfunction severity and consistent estimates of epidemiological measures [7, 8]. However, there is insufficient evidence to support their widespread application in critical care [9, 10]. Furthermore, in critically ill patients, renal dysfunction severity can also be evaluated by combining renal function with functional parameters of other organs (e.g., the Sequential Organ Failure Assessment (SOFA) score) [11].

In evidence-based medicine, multicenter, prospective, randomized controlled trials (RCTs) are the gold standard for evaluating treatment benefits and ensuring the effectiveness of interventions. Patient-centered outcomes, such as mortality, are most often the preferred evaluated outcomes [12]. While there is currently agreement on how to classify renal dysfunction in critically ill patients [13], the application frequency of this new classification system in RCTs has not previously been evaluated. In this study, we aim to assess the definition of renal dysfunction in multicenter RCTs involving critically ill patients that included mortality as a primary endpoint. In addition, we evaluated the criteria used to determine the severity and progression of kidney injury.

Methods
Search strategy and eligibility
A comprehensive search was conducted for publications reporting multicenter RCTs involving adult patients in intensive-care units (ICUs), with mortality as a primary outcome. The search was conducted in the MEDLINE database via the PubMed interface, including articles in the core clinical journals subset published May 2004 to December 2017 (In the list below). MEDLINE offers the “Core Clinical Journals” filter to limit searches to clinically useful journals [14, 15]. Eligibility assessment and data abstraction were performed independently in a non-blinded, standardized manner by two reviewers. Inter-rater reliability was evaluated using the kappa statistic. Discrepancies in methodological quality assessment and final classification of the RCTs were resolved by consensus among the authors. Comparison parameters included the definition and exclusion of patients with renal dysfunction, baseline serum creatinine levels, proportions of trial participants with renal dysfunction, and subgroup analyses involving acute renal dysfunction.

- 01 “intensive care”[MeSH Terms] OR Intensive care[Text Word]
- 02 “critical care”[MeSH Terms] OR critical care[Text Word]
- 03 (“critical illness”[TIAB] NOT Medline[SB]) OR “critical illness”[MeSH Terms] OR critically ill[Text Word]
- 04 “sepsis”[MeSH Terms] OR sepsis[Text Word]
- 05 “artificial respiration”[Text Word] OR “respiration, artificial”[MeSH Terms] OR mechanical ventilation[Text Word]
- 06 “adult respiratory distress syndrome”[Text Word] OR “respiratory distress syndrome, adult”[MeSH Terms] OR A RDS[Text Word]
- 07 (#01OR#02OR#03OR#04OR#05OR#06)
- 08 “randomized controlled trial”[Publication Type] OR “randomized controlled trials”[MeSH Terms] OR “randomized controlled trial”[Text Word] OR “randomised controlled trial”[Text Word]
- 09 #07 AND #08
- 10 (“Multicenter Studies”[MeSH] OR “Multicenter Study”[Publication Type]) OR multicenter[All Fields]
- 11. End Point Mortality
- 12 #09 AND #10

Data extraction
The following data were extracted: (1) subject of study, (2) number of patients, (3) number of centers, (4) conditions studied, (5) allocation concealment, (6) exclusion of chronic kidney disease, (7) exclusion of acute renal dysfunction, (8) chronic kidney disease (CKD) criteria, (9) baseline acute renal dysfunction criteria, and (10) acute renal dysfunction as outcome (11) mortality. Two authors (RHP and PB) evaluated the selected studies for quality using the Consolidated Standards of Reporting Trials (CONSORT) checklist.

Statistical analysis
Analyses were performed in SPSS 21.0 (SPSS, Inc.). Categorical variables are described as number (percentage).

Results
The selection and exclusion of RCTs are summarized in Fig. 1. Inter-observer agreement among the reviewers for the selection and final classification of the studies was high, with a kappa statistic of 0.86. From 418 separate articles, 46 multicenter RCTs (including both single-continent and
multi-continent settings) with a primary end point related to mortality were included [16–61]. Of these, 5 showed a beneficial effect of the trial intervention on mortality, whereas 41 demonstrated a neutral effect (Table 1).

CKD chronic kidney disease, PEEP positive end-expiratory pressure; SOFA sequential organ failure assessment, MV mechanical ventilation, MODS multiple organ dysfunction score, GFR glomerular filtration rate; LODS logistic organ dysfunction score, UO urine output, RRT renal replacement therapy, KDIGO Kidney Disease Improving Global Outcomes; RIFLE Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease, TAK-242 a small-molecule inhibitor of Toll-like receptor-4-mediated, ARDS acute respiratory distress syndrome, IABP intraaortic balloon pump, Cr creatinine

The distribution of the number of studies per year of publication, stratified by the acute renal dysfunction criteria used as a baseline and outcome measure is described in Figs. 2a and b, respectively (Fig. 2).

**Conditions studied**

A wide range of conditions in critically ill patients was studied in the 46 RCTs, including sepsis (13 RCTs), acute respiratory distress syndrome (11 RCTs), shock (5 RCTs), nutrition (4 RCTs), anemia (5 RCTs), surgery (3 RCTs), respiratory failure (2 RCTs), pneumonia (2 RCTs), renal replacement therapy (1 RCT), and quality improvement (1 RCT).
| Study                                      | First author         | Number | Centers | Area | CKD excluded | Acute renal dysfunction excluded | CKD criteria | Baseline acute renal dysfunction criteria | Acute renal dysfunction as Outcome | Mortality |
|--------------------------------------------|----------------------|--------|---------|------|--------------|----------------------------------|--------------|------------------------------------------|-----------------------------------|-----------|
| Norepinephrine plus dobutamine vs epinephrine in septic shock (2007) | D Annane [32]       | 330    | 19      | Drug | Yes          | No                               | McCabe       | SOFA/RRT                                | NA                                               | 400%      |
| Hydrocortisone in septic shock (2008)     | CL Sprung [27]       | 499    | 52      | Drug | Yes          | No                               | NA           | UO < 0.5 mL/kg/h for > 1 h or SOFA     | NA                                               | 39.2%     |
| Intensive insulin therapy in severe sepsis (2008) | FM Brunkhorst [30]  | 600    | 18      | Drug | No           | Yes                              | No           | NA                                       | 2 × Cr or RRT                                | 24.1%     |
| PEEP setting in acute lung injury and ARDS (2008) | A Mercat [49]       | 767    | 37      | MV   | No           | No                               | No           | NA                                       | SOFA                                             | 31.2%     |
| Vasopressin vs norepinephrine infusion in septic shock (2008) | JA Russell [37]     | 802    | 27      | Drug | Yes          | No                               | NA           | SOFA                                     | Brussels                                       | 43.9%     |
| Ventilation strategy in acute lung injury and ARDS (2008) | MD Meade [52]       | 983    | 30      | MV   | Yes          | No                               | NA           | No                                       | No                                               | 36.4%     |
| Exogenous surfactant in acute lung injury and the ARDS (2009) | J Kesecioglu [26]   | 418    | 67      | Drug | No           | No                               | No           | NA                                       | SOFA or LODS                                  | 24.5%     |
| TAK-242 in severe sepsis (2010)           | TW Rice [20]         | 274    | 93      | Drug | Yes          | Yes                              | NA           | SOFA                                     | SOFA                                             | 170%      |
| Neuromuscular blockers in early ARDS (2010) | L Papazian [31]     | 340    | 20      | Drug | Yes          | No                               | NA           | SOFA                                     | SOFA or Cr > 2                               | 31.6%     |
| Prone positioning in moderate and severe ARDS (2010) | P Taccone [50]      | 342    | 25      | MV   | No           | No                               | No           | NA                                       | SOFA                                             | 31.0%     |
| Early lactate-guided therapy (2010)       | TC Jansen [39]       | 344    | 4       | Protocol | No          | No                               | No           | NA                                       | SOFA or RRT                                  | 33.9%     |
| Corticosteroid and intensive insulin therapy in septic shock (2010) | D Annane [22]       | 509    | 11      | Drug | No           | No                               | No           | NA                                       | SOFA                                             | 42.9%     |
| Dopamine and norepinephrine in the treatment of shock (2010) | D De Backer [21]    | 1679   | 8       | Drug | Yes          | No                               | No           | NA                                       | SOFA or RRT                                  | 520%      |
| Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia (2011) | RG Wunderink [34]  | 2138   | 188     | Drug | Yes          | No                               | RRT          | SOFA or Cr > 3 or RRT                   | No                                               | 180%      |
| Intravenous β-2 agonist in acute respiratory distress syndrome (2012) | SF Gao [53]         | 326    | 46      | Drug | Yes          | No                               | No           | Critical care minimum dataset            | NA                                               | 340%      |
| IABP for myocardial infarction with cardiogenic shock (2012) | H Thiele [42]       | 600    | 37      | Protocol | No          | No                               | NA           | UO < 30 mL/h                             | GFR                                              | 39.7%     |
| Hydroxyethyl vs Ringer's acetate in severe sepsis (2012) | A Perner [28]       | 798    | 36      | Drug | Yes          | No                               | No           | NA                                       | SOFA or RRT or 2 × Cr or RIFLE                 | 51.0%     |
| Drotrecogin alfa in septic shock (2012)   | VM Ranieri [23]      | 1697   | 208     | Drug | Yes          | No                               | No           | NA                                       | SOFA                                             | 26.4%     |
Table 1 Description of the randomized controlled trials (Continued)

| Study                                                                 | First author          | Number | Centers | Area | Blinded | CKD excluded | Acute renal/dysfunction excluded | CKD criteria | Baseline acute renal dysfunction criteria | Acute renal dysfunction as Outcome | Mortality |
|----------------------------------------------------------------------|-----------------------|--------|---------|------|---------|--------------|-------------------------------|-------------|-------------------------------------------|-----------------------------------|-----------|
| Hydroxyethyl vs saline for fluid resuscitation (2012)               | JA Myburgh [29]       | 300    | 26      | Drug | Yes     | No           | No                            | McCabe      | SOFA                                      | No                                | 21.2%     |
| Statin in patients with ventilator associated pneumonia (2013)      | L Papazian [24]       | 300    | 26      | Drug | Yes     | No           | No                            | McCabe      | SOFA                                      | No                                | 47.6%     |
| Recombinant human activated protein C in septic shock (2013)        | D Annane [33]         | 411    | 24      | Drug | Yes     | No           | No                            | McCabe      | SOFA                                      | SOFA                              | 32.8%     |
| Prone positioning in ARDS (2013)                                    | C Guérin [51]         | 474    | 27      | MV   | No      | No           | No                            | McCabe      | SOFA                                      | SOFA                              | 47%       |
| High-frequency oscillation for early ARDS (2013)                    | ND Ferguson [48]      | 500    | 27      | MV   | No      | No           | No                            | NA          | No                                        | No                                | 41.7%     |
| High-frequency oscillation for ARDS (2013)                          | D Young [47]          | 795    | 29      | MV   | No      | No           | No                            | NA          | No                                        | No                                | 30.8%     |
| Effect of early vs late tracheostomy (2013)                         | D Young [41]          | 909    | 72      | Protocol | No         | No           | No                            | NA          | No                                        | No                                | 32.4%     |
| Glutamine and antioxidants in critically ill patients (2013)        | D Heyland [38]        | 1223   | 40      | Nutrition | Yes       | No           | No                            | NA          | SOFA or RRT                               | 22.8%     |
| Early parenteral nutrition in critically ill patients (2013)        | GS Doig [16]          | 1372   | 31      | Nutrition | No        | No           | No                            | RRT         | No                                        | SOFA or RRT                         | 25.4%     |
| Colloids vs crystalloids in hypovolemic shock (2013)                | D Annane [23]         | 2857   | 57      | Drug | No      | Yes          | No                            | McCabe      | SOFA                                      | No                                | 42%       |
| Perioperative goal-directed hemodynamic optimization in abdominal surgery (2014) | D Pestaña [43]       | 132    | 6       | Protocol | No         | No           | No                            | NA          | No                                        | No                                | 33.6%     |
| Perioperative, cardiac output-guided hemodynamic therapy algorithm in gastrointestinal surgery (2014) | RM Pearse [40]       | 734    | 17      | Protocol | Yes       | No           | Cr >14                        | No          | 2x Cr or Cr <0.5 mL/12 h                   | 325%     |
| Rosuvastatin for sepsis-associated ARDS (2014)                      | NHLBI ARDS Network [35]| 745     | 44      | Drug | Yes     | No           | No                            | RRT         | SOFA                                      | No                                | 285%      |
| High vs low blood-pressure target in septic shock (2014)            | P Asfar [36]          | 776    | 29      | Drug | No      | No           | No                            | RRT         | Cr > 1.9 or 500 ml/24 h                   | 2x Cr or RRT                         | 340%      |
| Lower vs higher hemoglobin in septic shock (2014)                   | LB Holst [45]         | 998    | 32      | Transfusion | No         | No           | No                            | RRT         | SOFA                                      | NA                                | 430%      |
| Album replacement in patients with severe sepsis or septic shock (2014) | P Caironi [19]        | 1781   | 100     | Drug | No      | No           | No                            | NA          | SOFA                                      | SOFA                              | 43.6%     |
| Trial route of early nutritional support in critically ill adults (2014) | SE Harvey [18]        | 2388   | 33      | Nutrition | No         | No           | No                            | RRT         | SOFA                                      | RRT                               | 33.1%     |
| Noninvasive ventilation vs oxygen therapy in immunocompromised patients with ARDS (2015) | V Lemiède [46]       | 374    | 28      | MV   | No      | No           | No                            | Charlson    | SOFA                                      | SOFA                              | 24.1%     |
| Study | First author | Number | Centers | Area | Blinded | Randomization | CKD excluded | Acute renal dysfunction criteria | Baseline acute renal dysfunction | Outcome | Acute renal dysfunction as | Mortality |
|-------|--------------|--------|---------|------|---------|---------------|--------------|---------------------------------|-------------------------------|---------|--------------------------|-----------|
| Acute renal dysfunction excluded | YM Arabi [17] | 894 | 7 | Nutrition | No | No | No | No | NA | SOFA | SOFA | 27.2% |
| Age of transfused blood in critically ill adults | J Lacroix [44] | 2510 | 64 | Transfusion | Yes | No | No | No | NA | MODS | MODS | 37% |
| Renal-replacement therapy in the intensive care unit (2016) | S Gaudry [54] | 620 | 31 | RRT | No | No | Yes | No | Yes | KDIGO | KDIGO/RRT | 48.5% |
| Sodium selenite and procalcitonin-guided therapy in severe sepsis or septic shock (2016) | F Bloos [55] | 1180 | 33 | Drug | No | No | No | No | No | No | No | 28.0% |
| Quality improvement intervention with daily checklist in critically ill patients (2016) | AB Cavalcanti [56] | 6877 | 118 | Daily checklist | No | No | No | No | No | No | No | 32.9% |
| Recruitment and titrated PEEP vs low PEEP on mortality in ARDS (2017) | ART Group [57] | 548 | 14 | Drug | No | No | Yes | No | No | No | No | 12.9% |
| Age of red cells for transfusion and outcomes in critically ill patients (2016) | G Landoni [58] | 548 | 14 | Daily checklist | No | No | Yes | No | No | No | No | 12.9% |
| Levosimendan after cardiac surgery (2017) | F Bloos [59] | 491 | 9 | Drug | Yes | No | No | No | No | No | No | 28.0% |
| Restriction vs liberal transfusion in cardiac surgery (2017) | AJ Cooper [60] | 1008 | 9 | Transfusion | Yes | No | Yes | No | No | No | No | 55.0% |
| Restriction vs liberal transfusion in cardiac surgery (2017) | CD Mazer [61] | 1008 | 9 | Transfusion | Yes | No | Yes | No | No | No | No | 55.0% |
| Short-term vs long-term blood storage on mortality (2017) | NM Heddle [62] | 24743 | 4 | Transfusion | No | No | No | No | No | No | No | 91.7% |
to the parameters used to measure renal function, primarily creatinine concentration and urine output, because these parameters are frequently influenced by comorbidities, nutritional status, fluid overload and the overall severity of critical illness [62].

A single definition of acute renal dysfunction would be useful for clinical practice, research, and public health [13]. This definition has been rapidly changing in the literature since 2004 with the introduction of the RIFLE, AKIN, and KDIGO classification systems. These classifications were developed based on both evidence and consensus [63]. However, our findings show that with a few exceptions, they were not applied in RCTs with mortality as a primary outcome published in the period of this study. Furthermore, these systems were not widely used for defining or evaluating renal dysfunction as a secondary endpoint. These findings may raise concerns about the evidence-based use of these classification systems in the clinical management of critically ill patients. Nevertheless, it is important to notice that there was an apparent increase in the utilization of these scores in recent years (2016 and 2017).

Although the acute renal dysfunction (RIFLE/AKIN/KDIGO) classification systems have been compared and validated [64], they do have certain limitations. First, the use of small changes in serum creatinine levels to diagnose AKI is limited by the high rates of false-positive diagnoses caused by the inherent variability of serum creatinine levels in patients with higher baseline values, thus potentially misclassifying patients with CKD [65]. Second, in contrast to individual measurements, efforts to determine the trajectory of serum creatinine levels can identify AKI sub-phenotypes with different mortality risks, even among patients with AKI of similar severity. These AKI sub-phenotypes might define patients at risk of poor outcomes (i.e., those with non-resolving AKI), who might benefit from novel interventions [66]. Third, renal dysfunction definitions that require a reference creatinine value to analyze baseline renal function should utilize a value that reflects steady-state kidney function prior to an AKI episode. When such reference values are not available, surrogate estimates are required, and these can affect the accuracy of the determination [67]. In contrast, the simplicity of the SOFA score and the objectivity of the variables required for its calculation make it useful for repeated measurements of the degree of organ dysfunction or failure [68].

The renal SOFA score was the most commonly used system to quantify renal function at baseline or as a secondary outcome. It may be more convenient to study changes in the SOFA score over time. Such changes have been assessed in critically ill patients over 48 h or during treatment [70] and have also been used to evaluate the degree of organ dysfunction in sepsis [63]. In addition to assessing patient status, renal criteria can be used for prognosis. An early and sequential evaluation pattern (using any of the various scoring systems) has been shown to be a superior approach for prognostic scoring in critically ill patients who develop renal dysfunction compared with a single assessment at any time point during an ICU admission or stay [71]. Similarly, in patients with kidney injury, measuring changes in the SOFA score in the first 24 h of RRT can identify patients at high risk of mortality [72]. In contrast, individual SOFA scores are poor at predicting early (7 day) mortality in patients with septic AKI who require continuous RRT [73].

In addition to the new definitions of renal dysfunction, the SOFA score has been validated as a tool for assessing sequential organ dysfunction and is a good prognostic indicator. Furthermore, this score is familiar to critical care physicians and has been used for years in critical care settings and for different clinical conditions [69]. To date, no study has directly compared SOFA with RIFLE/AKIN/KDIGO; however, the use of RIFLE criteria improved the performance of the Acute Physiology and Chronic Health Evaluation disease classification system II (APACHE II) score in predicting mortality in critically ill patients [74]. The prognostic value of a hypothetical score that
combines RIFLE/AKIN/KDIGO criteria with the SOFA score, perhaps by replacing renal SOFA criteria variables with KDIGO criteria variables, is a matter of future research.

To our knowledge, the present manuscript is the first to describe the characterization of acute renal dysfunction in RCTs of critically ill patients. We have utilized an extensive search covering a period of 13 years following publication of current renal dysfunction definitions.

Nonetheless, our study does have several limitations. First, we have limited our sample to papers published in high-impact journals because these are typically multicenter studies with a better opportunity for impacting clinical practice [75]. We defined high-impact journals as those included in the MEDLINE core clinical journals subset [14]. The core clinical journals subset is an easy filter to apply. Using this filter, a MEDLINE search can focus on a set of journals selected for high quality and clinical utility, which may aid in the reproducibility of our findings, though we do recognize that there have been controversies as to the actual clinical utility of this subset [15]. However, because the new definitions of renal dysfunction are used at similar frequencies among the major journals, it is reasonable to assume that the addition of extra journals would not have meaningfully changed our results. In agreement with our methodology, other recently published reviews have utilized similar procedures [76, 77]. Nevertheless, this selection procedure may result in biases because papers published in journals with a lower impact factor may characterize renal dysfunction differently. Another limitation is that because we relied on published material as the typical information source for clinicians, we cannot exclude the possibility that some trials reported characterizations of renal dysfunction that differed from their original protocols [78].

**Conclusion**

The presence of renal dysfunction was included as a baseline patient characteristic and as an outcome measure in most multicenter RCTs involving critically ill patients with mortality as a primary endpoint that were published in core clinical journals in the study period. The analyzed RCTs generally defined acute renal dysfunction using the SOFA score, with a less frequent utilization of the RIFLE, AKIN and KDIGO classification systems. There is a need for further evaluation of the validity and barriers for utilization of each score to better inform clinical practice.

**Abbreviations**

AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; APACHE: Acute Physiology and Chronic Health Evaluation disease classification system; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; ICUs: Intensive care units; KDIGO: Kidney Disease Improving Global Outcomes; RCTs: Randomized controlled trials; RIFLE: Risk, Injury, Failure, Loss, End-stage renal disease; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors’ contributions**

R-P and PRB contributed to the design, acquisition, analysis, and interpretation of data and drafting and revising the manuscript. JGRR, AG, JC, and EM contributed to interpretation of data and drafting and revising the manuscript. All authors have read and approved the final version of this manuscript.

**Authors’ information**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

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