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# Defibrillation strategies for patients with refractory ventricular fibrillation: A systematic review and meta-analysis

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ABSTRACT

*Aim:* The aim of this study was to summarize the existing evidence about the effectiveness of double defibrillation (DD) in comparison to standard defibrillation for patients with refractory ventricular fibrillation (RVF). DD encompasses double "sequential" external defibrillation (DSeq-D) and double "simultaneous" defibrillation (DSim-D), with the study also shedding light on the respective effects of DSeq-D and DSim-D.

*Methods:* Investigators systematically searched PubMed, EMBASE and Cochrane Central databases for randomized controlled trials (RCTs) and cohort studies from their inception until June 06, 2024. The rate of survival to hospital discharge was the primary outcome, while the incidence of return of spontaneous circulation (ROSC), termination of ventricular fibrillation (VF), survival to hospital admission and good neurologic outcome were secondary outcomes. Relative ratios (RR) and 95% confidence intervals (CIs) were calculated for each outcome. Heterogeneity was assessed using *I* square value.

*Results:* A total of 6 trials, comprising 1360 patients, were included. One was an RCT, and five were observational cohort studies. The RCT showed that, compared to standard defibrillation, DSeq-D was associated with higher incidences of survival to hospital discharge, termination of VF, ROSC and good neurologic outcome. However, the pooled results of cohort studies found no benefit of DD over standard defibrillation in survival to hospital discharge (RR, 0.91; 95% CI, 0.46–1.78), nor in secondary outcomes. Furthermore, subgroup analysis suggested DSim-D was linked with lower ROSC rate compared to standard defibrillation (RR, 0.65; 95% CI, 0.49–0.86), while there was no significance between DSeq-D and standard defibrillation (RR, 1.00; 95% CI, 0.70–1.42).

*Conclusions:* The benefit of DSeq-D in survival to hospital discharge for RVF patients was found in the RCT, but not in cohort studies. Additionally, DSim-D should be applied with greater caution for RVF patients. Further validation is needed through larger-scale and higher-quality trials.

*Trial registry:* INPLASY; Registration number: INPLASY202340015; URL: https://inplasy.com/



## 1. Introduction

Cardiac arrest is the third primary cause of death in developed nations, with almost one-third resulting from shockable rhythm, for instance, pulseless ventricular tachycardia (pVT) or ventricular fibrillation (VF) [1]. Shockable rhythm is associated with higher survival rate than non-shockable ones [2,3]. Unfortunately, nearly half of these patients still present with VF despite multiple defibrillation attempts, which is known as refractory VF (RVF) [4-6]. Previously, RVF was defined as persistent VF without response to five standard shocks [7-9], while in recent years, it has been defined as VF that fails to terminate after three or more standard defibrillation attempts [10-12]. With the deepening of the understanding of RVF, advances in treatment are also constantly progressing. Consequently, new defibrillation strategies, such as double defibrillation (DD), have been studied to improve patients' prognosis [12].

In standard defibrillation, a single defibrillator is used, with the defibrillation pads placed on the anterior-lateral parts of the chest [13]. On

*Abbreviations:* RVF, refractory ventricular fibrillation; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; DD, double defibrillation; DSeq-D, double sequential external defibrillation; DSim-D, double simultaneous defibrillation; RCTs, randomized clinical trials; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; NOS, Newcastle-Ottawa Scale; IQR, inter quartile range; SD, standard deviation; RR, relative ratios; CIs, confidence intervals; vs., versus.

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the other hand, DD involves the using two defibrillators positioned in two different locations: anterior-lateral and anterior-posterior. Depending on the defibrillation timing of the two defibrillators, DD includes double "simultaneous" defibrillation (DSim-D) and double "sequential" external defibrillation (DSeq-D). In DSim-D, both defibrillators discharge simultaneously, while in DSeq-D, they discharge sequentially [13,14].

In recent years, DD has been studied regarding the use in patients with RVF [15-17], and many theories supported its application, including "power theory", "setting up theory" and "multiple vector theory" [11]. The use of DSeq-D was associated with better prognosis compared with standard defibrillation for RVF patients in the recently published randomized controlled trial (RCT), the double sequential external defibrillation for refractory ventricular fibrillation (DOSE VF) trial [10,13]. Additionally, some case reports have demonstrated successful defibrillation using DD for RVF patients [18,19]. However, the effectiveness of DD was not always clear in previously published studies [9,20-25], and previous reviews did not find sufficient evidence to support the application of DD [26-29]. Furthermore, no studies have been conducted regarding the difference of DSeq-D and DSim-D. Consequently, this study was performed to further update and consolidate the current evidence about the effectiveness of DD comparing with standard defibrillation in RVF patients, and to clarify the respective effects of DSeq-D and DSim-D.

## 2. Methods

This research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. The study's protocol was registered at https://inplasy.com/, with INPLASY202340015 as the registration number.

### 2.1. Relevant research screening

Two investigators (JZY and YWY) systematically searched the PubMed, Cochrane Central, and EMBASE databases independently, for English published articles from their inception until June 06, 2024. Any discrepancies were resolved through discussions with a third investigator (HYL). A combination of "All Fields/All Text" and "Mesh/Emtree terms" were used for the search, including "refractory ventricular fibrillation" and "double/dual defibrillation". The specific search strategy is available in Additional file 1. The flow chart diagram for filtering relevant research according to the inclusion and exclusion criteria is illustrated in Fig. 1.

### 2.2. Inclusion and exclusion criteria

The following inclusion criteria determined the eligibility of studies: (1) Population: the study populations were adult RVF patients; (2) Intervention: the intervention was DD, including DSeq-D and DSim-D; (3) Comparison: the control group was treated with standard defibrillation; (4) Outcome: at least one of the study outcomes has been reported; (5) Study design: the types of studies were RCTs or cohort studies; (6) English written articles.

The studies were eliminated based on the following exclusion criteria: (1) Population: the study populations were not RVF patients; instead, they included patients with conditions such as atrial fibrillation; (2) Intervention: the interventions implemented were other defibrillation strategies, such as vector-change defibrillation; (3) Comparison: the studies either lacked a control group or the control group did not undergo standard defibrillation; (4) Outcome: neither primary nor secondary study outcomes were reported; (5) Study design: the study was case reports or case series, or only abstracts of the original

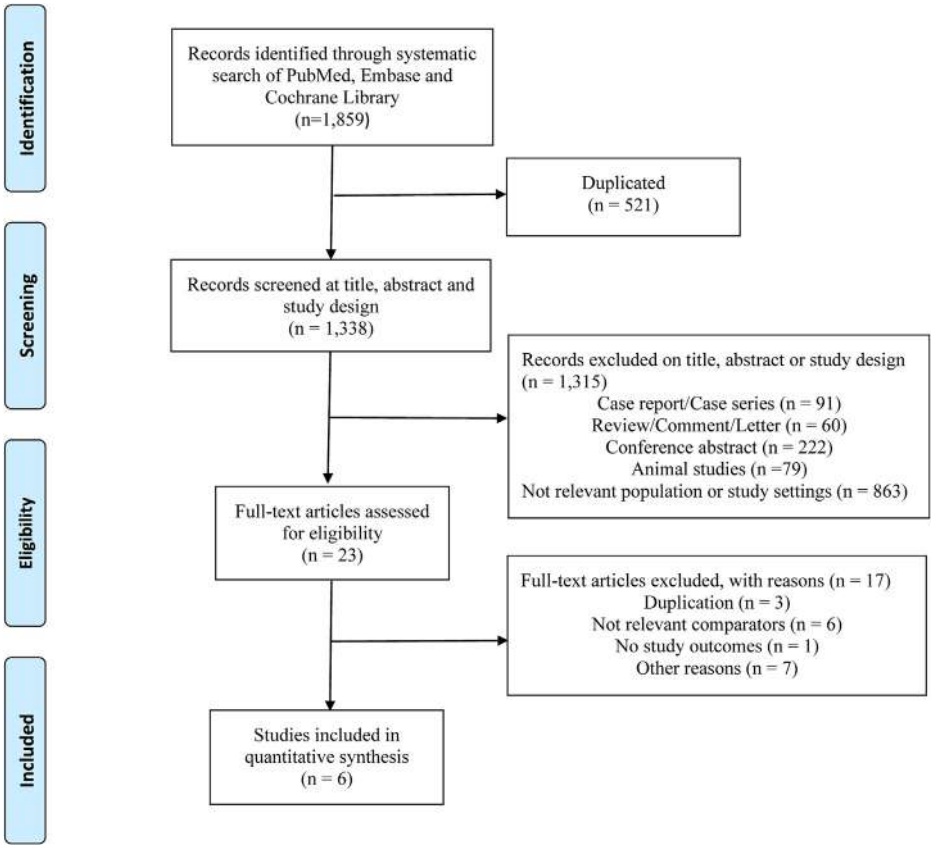


**Fig. 1.** Flowchart of the study selection process.

research were available, or only citations or reports of the research found in other publications, and full text of the articles were unavailable.

### 2.3. Study outcomes

The rate of survival to hospital discharge was the primary outcome. The secondary outcomes encompassed the incidence of return of spontaneous circulation (ROSC), termination of VF, survival to hospital admission and good neurologic outcome (modified Rankin scale score ≤ 2). In addition, patient demographics and event characteristics such as age, gender, bystander cardiopulmonary resuscitation (CPR), the median time from the initial call to first shock, the number of all defibrillation shocks, and the number of standard defibrillation shocks were also subjected to statistical analysis.

### 2.4. Study selection and data extraction

Two independent researchers (JZY and YWY) selected all the available articles following the inclusion and exclusion criteria. Any discrepancies were resolved through discussions between two independent researchers, and, if it was necessary, by a third researcher (YXG). The relevant information was drawn from the original articles, encompassing the last name of the first author, study period, publication year, study design type, the host country of the research, number of experimental and control groups, study populations, and methods of DD.

### 2.5. Risk of bias evaluation

The RCT' risk of bias was evaluated according to the Cochrane Collaboration principles, covering random sequence generation, allocation concealment, participants and personal blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. Moreover, the Newcastle-Ottawa Scale (NOS) [31] was utilized to assess cohort studies' risk of bias, with the items covering selection of cohorts (including the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure to implants and demonstration that outcome of interest was not present at start of study), comparability of cohorts (comparability of cohorts on the basis of the design or analysis), and outcome assessment (including Assessment of outcome, follow up long enough for outcomes to occur and adequacy of follow up of cohorts). According to the NOS scale, there could be up to one point per entry for selection and outcome assessment, and up to two points for comparability , resulting in a total score of nine.

Two researchers (YZ and DY) independently evaluated the risk of bias for each included trial according to the evaluation criteria. In case of any disagreements, they consulted with a third researcher for resolution.

### 2.6. Statistical analysis

In the meta-analysis, if the continuous variables were presented as median (inter quartile range, IQR), the normal-based methods were used to transform them to mean (standard deviation, SD), unless the data were significantly skewed away from normality [32-34]. Heterogeneity was assessed using $I^2$ and $P$ values, with $I^2$ values indicating low (<50%), moderate (51%–75%), or high (≥76%) variability due to heterogeneity rather than sample error, respectively. When heterogeneity was low, the fixed-effects model was applied to calculate the combined relative ratio (RR) and 95% confidence intervals (CIs) for each outcome; if not, the random-effects model was used. Sensitivity analysis was carried out by excluding each included trial individually to assess the effect on the pooled RR and 95% CIs to detect the robustness of the results when heterogeneity was high. Statistical analyses were accomplished using Review Manager 5.3 and Stata 16.0 software.

## 3. Results

### 3.1. Screening of relevant research

According to the retrieval strategy, a total of 1859 articles were screened, out of which 521 duplicates were identified. Further screening based on titles, abstracts, and study design led to the elimination of 1315 articles due to reasons such as irrelevant population or study settings, animal studies, case reports, or case series, among others. After reviewing the full text, 17 trials were further excluded due to duplication, unrelated comparators, irrelevant study outcomes, or other reasons. Finally, a total of 6 articles, consisting of one RCT [10] and five observational cohort studies [14,22-25] were incorporated in the systematic review and meta-analysis (Fig. 1).

### 3.2. Study characteristics

In total, this study examined the outcomes of 1360 patients with RVF, comprising 359 in the DD group and 1001 in the standard defibrillation group. The included studies consisted of five cohort trials [14,22-25] and one RCT [10]. Within the RCT, the designated strategy for DD was DSeq-D. Out of the five cohort studies, two [22,25] employed DSeq-D and three [14,23,24] utilized DSim-D for the DD group. Detailed information on the incorporated studies is tabulated in Table 1.

In addition, due to the inclusion of only one RCT, the DOSE VF study [10], the meta-analysis was performed only for the cohort studies, and the result of the DOSE VF trial was presented descriptively.

### 3.3. Risk of bias assessment

All the cohort studies received scores of six points or higher based on the NOS assessment (Additional file 2). The RCT' risk assessment of bias was also suggestive of low risk (Additional file 3).

### 3.4. Outcomes for DD compared with standard defibrillation

#### 3.4.1. Primary outcomes

*3.4.1.1. Rate of survival to hospital discharge.* The rate of survival to hospital discharge was reported in four cohort studies [14,23-25].In total, 13.8% of patients in the DD group and 15.2% of patents in the standard group survived to hospital discharge, suggesting no significant difference between the two groups (RR, 0.91; 95% CI, 0.46–1.78; $I^2$, 41%) (Fig. 2).

Of the four cohort studies, one trial [25] used DSeq-D and three trials [14,23,24] applied DSim-D in the DD group. The subgroup analysis revealed no significant differences between DSim-D and standard defibrillation in terms of survival to hospital discharge (17.5% vs. 17.4%; RR, 1.05; 95% CI, 0.46–2.39; $I^2$, 55%). The sole trial that implemented DSeq-D demonstrated a consistent outcome. (Fig. 2).

#### 3.4.2. Secondary outcomes

*3.4.2.1. Rate of ROSC.* Four cohort studies [22-25] examined the rate of ROSC. Spontaneous circulation was restored in 33.1% of patients in DD group and 41.8% in the standard group, revealing no statistically significant difference between the two groups (RR, 0.78; 95% CI, 0.59–1.02; $I^2$, 25%) (Fig. 3).

Of the four studies, two trials [22,25] used DSeq-D and two [23,24] performed DSim-D for defibrillation in the DD group. Subgroup analysis inferred no difference between DSeq-D and standard groups in terms of ROSC (31.0% vs. 31.3%; RR, 1.00; 95% CI, 0.70–1.42; $I^2$, 0%), while DSim-D was associated with a significantly lower rate of ROSC compared to the standard defibrillation (35.1% vs. 49.1%; RR, 0.65; 95% CI, 0.49–0.86; $I^2$, 0%) (Fig. 3).

*3.4.2.2. Rate of termination of VF.* The rate of termination of VF was assessed in one cohort study [22], which used DSeq-D as the

**Table 1**
Summary of included studies.

| Author(year) | Study Period | Study design | Country; MC/SC | No. of arms (New strategies vs. Standard) | Subjects | Methods of DD |
|---|---|---|---|---|---|---|
| Cheskes et al. (2022) | 2018.03–2022.05 | three-arm, cluster RCT | Canada; MC | DSeq-D (125) vs. Standard (136) | adult patients with RVF | DD: Three standard defibrillation + DSeq-D (a rapid sequential manner; 200 J or 360 J) |
| Cheskes et al. (2019) | 2015.01–2017.12 | retrospective cohort study | Canada; MC | DSeq-D (51) vs. Standard (201) | adult patients with RVF | DD: At least three standard defibrillation + DSeq-D (a rapid sequential manner) |
| Emmerson et al. (2017) | 2015.07–2016.12 | retrospective cohort study | England; SC | DSeq-D (45) vs. Standard (175) | adult patients with RVF | DD: 38 patient, ≥ 6 standard shocks + DSeq-D; 7 patients, <6 standard shocks + DSeq-D (sequential, approximately 3–4 s apart, 360 J) |
| Ross et al. (2016) | 2013.01–2015.12 | retrospective cohort study | America; SC | DSim-D (50) vs. Standard (229) | recurrent VF and RVF | DD: Unknown times of standard defibrillation + DSim-D (simultaneously, 200 J) |
| Beck et al. (2019) | 2013.01–2016.12 | retrospective cohort study | America; SC | DSim-D (71) vs. Standard (239) | adult patients with RVF | DD: At least three standard defibrillation + DSim-D (simultaneously, 360 J) |
| Kim et al. (2020) | 2016.01–2017.12 | retrospective cohort study | Korea; MC | DSim-D (17) vs. Standard (21) | adult patients with RVF | DD: At least three standard defibrillation + DSim-D (simultaneously, 200 J) |

RCT, randomized clinical trial; DD, Double defibrillation; DSeq-D, Double sequential external defibrillation; DSim-D, Double Simultaneous Defibrillation; VF, ventricular fibrillation; RVF, refractory ventricular fibrillation; SC, single center; MC, multicenter; VS., versus; No., number.

defibrillation strategy in the DD group. Termination of VF was achieved in 76.5% of patients in the DSeq-D group and 78.1% in standard group, showing similar rates between the two groups.

*3.4.2.3. Rate of survival to hospital admission.* Three eligible studies [14,23,24] reported the incidence of survival to hospital admission, and all used DSim-D in the DD group. It suggested no distinct difference between DSim-D and standard defibrillation in the rate of survival to hospital admission (43.0% vs. 41.7%; RR, 1.24; 95% CI, 0.60–2.55; $I^2$, 84%) (Fig. 4).

*3.4.2.4. Rate of good neurologic outcome.* Two included cohort studies [14,23] examined good neurologic outcome, both using DSim-D in the DD group. The result suggested no significant discrepancies between DSim-D and standard defibrillation groups in the rate of good neurologic outcome (16.3% vs. 11.2%, RR, 1.40; 95% CI, 0.32–6.21; $I^2$, 53%) (Fig. 5).

*3.4.3. Patient demographics and event characteristics*

We conducted a comprehensive analysis of patient demographics and event characteristics and found that the DD group was related to a higher proportion of male patients compared to the standard group (84.6% vs. 77.7%; RR, 1.09; 95% CI, 1.02–1.16; $I^2$, 10%). There were no notable discrepancies between DD and standard groups in terms of age (MD, −1.51; 95% CI, −3.68–0.65; $I^2$, 0%), the rate of bystander CPR (51.5% vs. 52.3%; RR, 0.98; 95% CI, 0.85–1.13; $I^2$, 28%), and the mean time from initial call to first defibrillation (MD, −0.49; 95% CI, −1.54–0.57; $I^2$, 0%). In addition, the DD group received a significantly higher number of all defibrillation shocks compared with the standard group (MD, 2.12; 95% CI, 1.56–2.67; $I^2$, 36%), while no differences were observed in the number of standard defibrillation shocks (MD, −0.20; 95% CI, −0.72–0.32; $I^2$, 0%). The pooled results were shown in Fig. 6.

*3.4.4. Results of the RCT*

In the DOSE VF trial [10], the DSeq-D was used as the defibrillation strategy in the DD group. The results showed that compared to standard defibrillation, DSeq-D was associated with higher rates of survival to hospital discharge (30.4% vs. 13.3%), ROSC (46.4% vs. 26.5%), termination of VF (84% vs. 67.6%) and good neurological outcomes (27.4% vs. 11.2%).

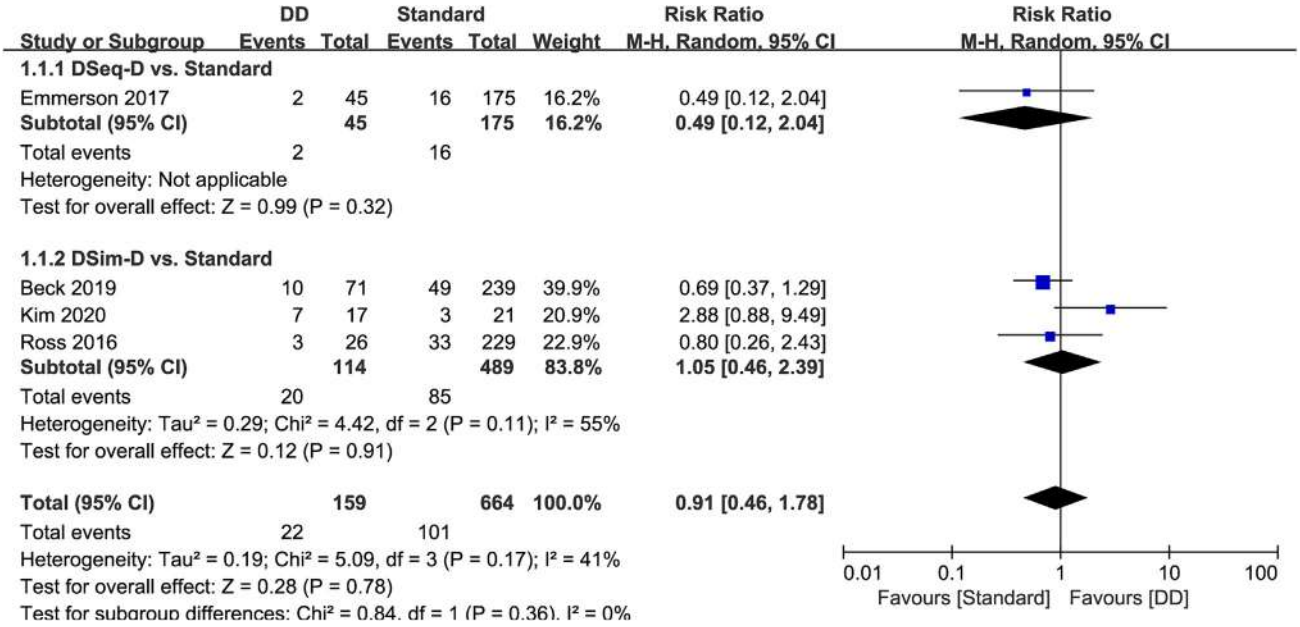


**Fig. 2.** DD vs. standard defibrillation (including subgroup analysis), outcome: survival to hospital discharge.

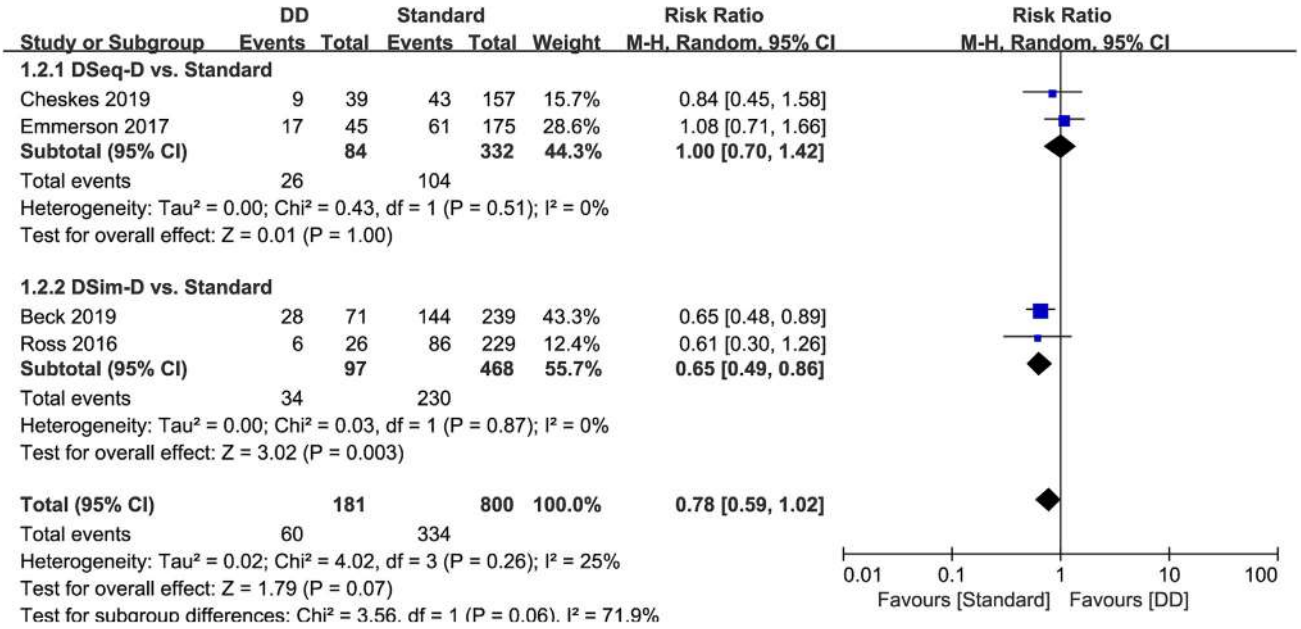


**Fig. 3.** DD vs. standard defibrillation (including subgroup analysis), outcome: ROSC.

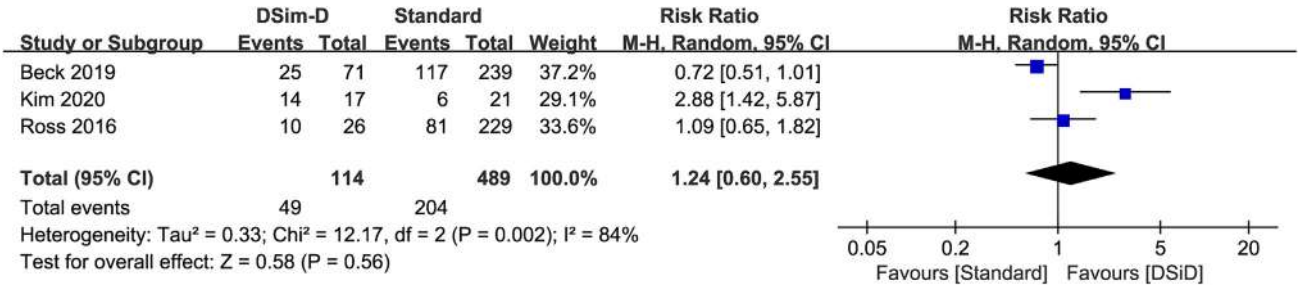


**Fig. 4.** DD (DSim-D) vs. standard defibrillation, outcome: survival to hospital admission.

### *3.5. Sensitivity analysis*

Sensitivity analysis was conducted by excluding each included article individually to assess the effect on the pooled RR and 95% CIs. The results indicated that the findings were credible and stable (Additional files 4 and 5 were the sensitivity analysis for the rate of survival to hospital discharge and survival to hospital admission, respectively).

## 4. Discussion

This is the first systematic review and meta-analysis to perform subgroup analysis for DSeq-D and DSim-D, and found DSim-D was linked with lower ROSC rate compared to standard defibrillation, suggesting that DSim-D should be applied more cautiously in RVF patients. Moreover, the pooled results of cohort studies revealed no advantage of DD over standard defibrillation in survival to hospital discharge or secondary outcomes. Notably, the DOSE VF study demonstrated that, compared to standard defibrillation, DSeq-D was associated with higher incidences of survival to hospital discharge, termination of VF, ROSC and good neurologic outcome. Larger-scale and higher-quality trials should be conducted to further investigate their effectiveness.

The results of the DOSE VF study differ significantly from the pooled results of cohort studies. There are three possible reasons for the notable difference, presented as follows:

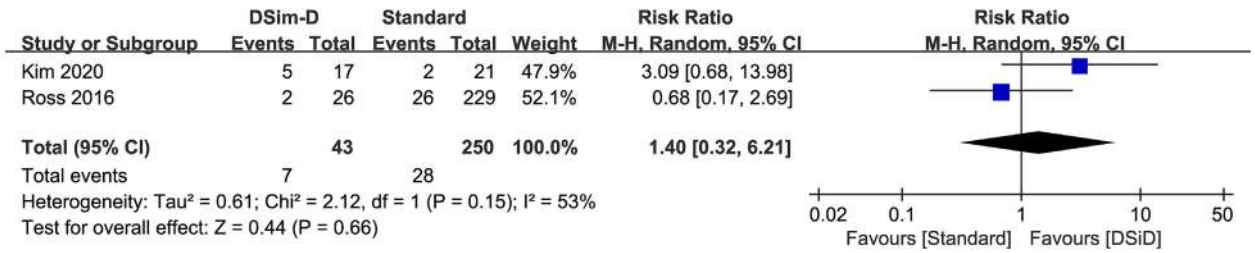


**Fig. 5.** DD (DSim-D) vs. standard defibrillation, outcome: good neurologic outcome.

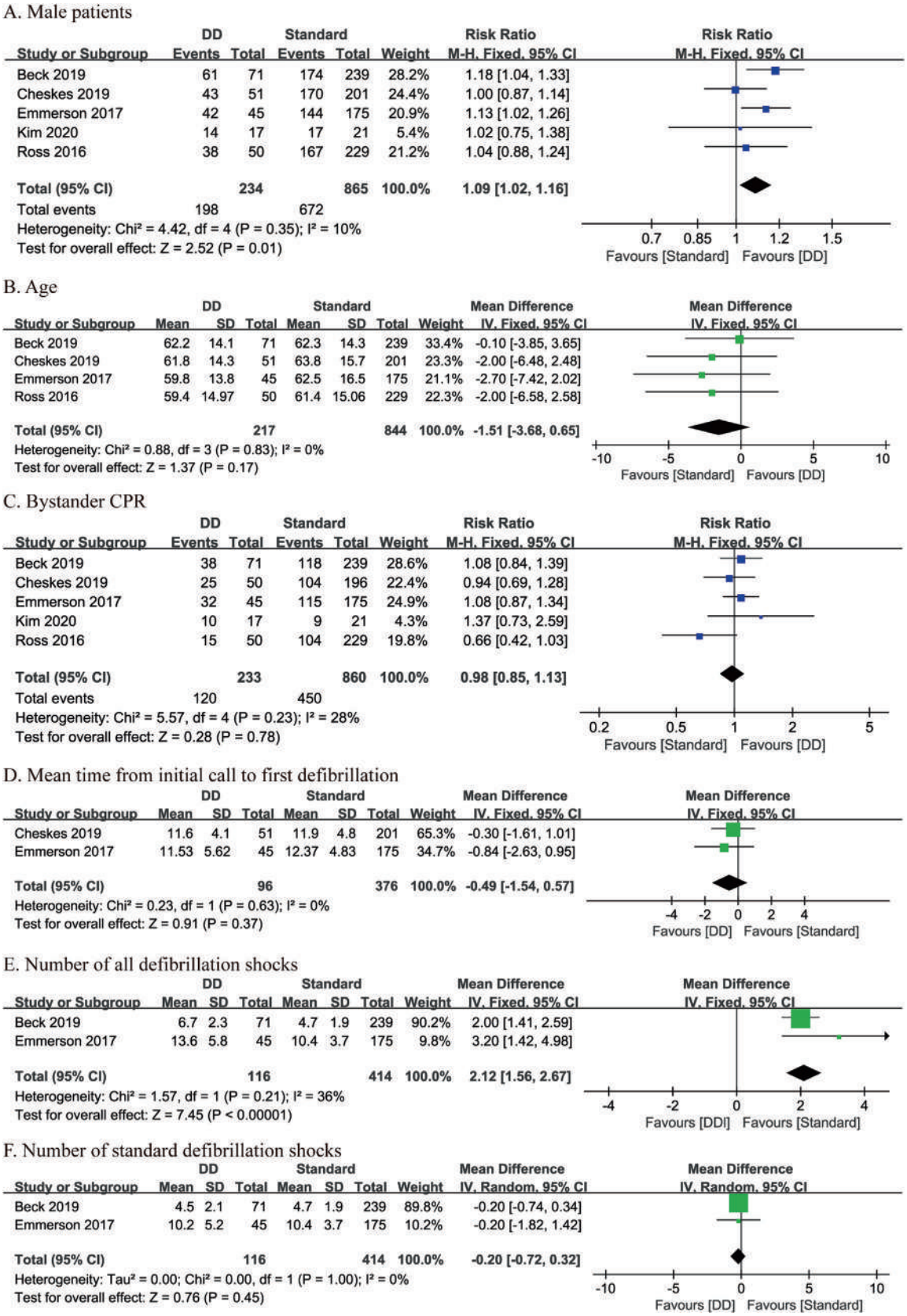


**Fig. 6.** DD vs. standard defibrillation, outcome: patient demographics and event characteristics (Figure legend: A, Male patients; B, Age; C, Bystander CPR; D, Mean time from initial call to first defibrillation; E, Number of all defibrillation shocks; F, Number of standard defibrillation shocks. CPR, cardiopulmonary resuscitation.)

Firstly, the timing of DD application varies across studies, with the DOSE VF study [10] performing DD at the fourth shock after the first three standard defibrillation attempts, while other observational studies applied DD relatively late. For instance, Emmerson et al. [25] reported that more than half of the patients received over six standard shocks before being treated with DD. Similarly, in Cheskes et al.'s retrospective study [22], most patients received DD on the seventh shock in the DD group, and the shock-based analysis indicated that when considering early defibrillation attempts, the VF termination rate was greater for patients undergoing DD compared to standard shocks. As several studies have shown, earlier DD might be linked to improved outcomes [10,22]. Therefore, DD should be administered following the failed first three standard defibrillation attempts, rather than as a "rescue" or late treatment after numerous shocks [35,36].

Secondly, the time interval for DSeq-D varies considerably. In the DOSE VF RCT, the time interval between the two defibrillators was described as being administered "in a rapid manner" [10], while in cohort studies, such as the one by Emmerson et al., the defibrillation interval for DSeq-D could be approximately 3–4 s apart [25]. Currently, there is no consensus regarding the defibrillation interval for DSeq-D. However, recent studies have reported improved rates of VF termination and ROSC when the DSeq-D interval was less than 75ms [37]. Due to limitations in measuring the exact time, the optimal DSeq-D interval has not yet been determined, highlighting the need for further research regarding this issue.

Finally, in the DOSE VF study, the crossover cluster RCT design greatly minimized the potential of treatment confounding factors in the study groups, which was not the case in observational studies [10]. Furthermore, the pooled results of cohort studies identified a higher proportion of male patients and a greater number of all defibrillation shocks in the DD group, indicating baseline data might be unmatched between the two groups. It is possible that patients in the DD group had more intractable RVF than those in the standard group, as the previous view supports DD as a last-resort treatment. Consequently, the DOSE VF RCT results seem more reliable from this perspective. However, the treatment effect in the RCT might be overestimated due to the trial's failure to achieve its planned sample size because of the Covid-19 pandemic [10]. Therefore, there remains an urgent need for large-scale RCTs to further investigate the effectiveness of DD [38].

The subgroup analysis in this study showed discrepancies in DSeq-D and DSim-D. There was no difference between DSeq-D and standard group in the rate of ROSC, which was lower in the DSim-D group. It seems that DSeq-D is more beneficial than DSim-D in patients with RVF. However, no studies have directly compared "simultaneous" with "sequential" defibrillation currently. The "setting up theory" suggested that sequential defibrillation might be more effective in terminating VF. This theory proposed that the first transthoracic current could lower the defibrillation threshold, making it easier for the second transthoracic current to successfully convert any remaining fibrillating myocytes [11]. Furthermore, simultaneous defibrillation might increase the risk of instrument damage, as reported in a survey of defibrillator damage during DD for RVF patients which showed all reported cases of defibrillator damage occurred using a simultaneous defibrillation technique [39]. Further studies are warranted to ascertain the safety and efficacy of "sequential" and "simultaneous" defibrillation techniques, in order to establish a standardized approach for the implementation of DD.

Although subgroup analysis was performed, the heterogeneity of some outcomes, such as survival to hospital admission, was still relatively high. Sensitivity analysis suggested the result was robust and credible, and the heterogeneity was mainly related to the "Kim 2020" trial [14]. This might be due to two aspects: firstly, the sample size of the "Kim 2020" trial was much smaller than that of the other two studies [14,23,24]; secondly, the patients' ethnicities were different. The patients included in Kim et al.'s study were Korean [14], while those in the other two studies were from America [23,24]. We look forward to more countries paying attention to this research area and conducting relevant studies to further clarify the effects of new defibrillation strategies in RVF patients on different ethnic groups.

In addition, it is worth noting that in the DOSE VF study, besides the comparison between DD and standard defibrillation, vector-change defibrillation and standard defibrillation were also compared. Vector-change defibrillation is an approach that involves switching the defibrillation pads from the standard position (anterior–lateral) to the anterior–posterior position [13]. This technique has the possibility to defibrillate a part of the ventricle myocytes that might fail to be fully defibrillated by the standard defibrillation [10]. The DOSE VF study demonstrated that, compared to standard defibrillation, vector-change defibrillation had a higher likelihood of survival to hospital discharge and termination of VF. However, the calculated fragility index suggests caution in interpreting these results, as they may be sensitive to changes in one patient's outcome. Additionally, a retrospective study for initial VF or pVT showed no significant difference in VF/pVT termination between vector-change and standard defibrillation [40]. Large-scale RCTs are necessary to further investigate the effectiveness of vector-change defibrillation in RVF patients. If the benefits of vector-change defibrillation could be ascertained, it might serve as an additional viable defibrillation strategy [10,41].

In general, the included studies are significantly valuable because they have not only laid the groundwork for exploring innovative defibrillation strategies for patients with RVF, but also prompted clinicians and researchers to focus on this field. However, these studies also carry several limitations. First, there's a noticeable deficiency of RCTs, with only the DOSE VF trial having been conducted so far, which did not meet the target number of participants. Second, the high degree of heterogeneity between observational studies, largely attributed to the varied implementation methods of DD, is another limitation. Consequently, it is essential to conduct larger-scale, multi-center studies of higher quality to further investigate the effectiveness and safety of DSeq-D and DSim-D, as well as to address unresolved issues, such as the optimal defibrillation interval for DSeq-D [42].

The present study had two main advantages: Firstly, it is the first systematic review and meta-analysis in which the DD group was divided into DSeq-D and DSim-D subgroups for analysis, illuminating the distinctions of the two methods and presenting a more comprehensive insight into the DD strategy. Secondly, by incorporating the most recent articles, the study offers a clearer perspective on the current state of research advancements in new defibrillation strategies.

This study also has several limitations: firstly, it was original literatures' secondary analysis, which inevitably result in heterogeneity between studies in terms of sample size and methods of defibrillation. The high heterogeneity could have influenced the statistical results to some extent. Secondly, most studies incorporated were observational studies, which could not avoid many confounding factors that might potentially affect the results.

## 5. Conclusions

This is the first systematic review and meta-analysis to perform subgroup analysis for DSeq-D and DSim-D, suggesting that DSim-D should be applied with greater caution in RVF patients. The benefit of DSeq-D in survival to hospital discharge for RVF patients could be found in the RCT, but not in cohort studies. Further validation is needed through larger-scale and higher-quality trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2024.07.059.

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## CRediT authorship contribution statement

**Jinzhou Yu:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Yanwu Yu:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Huoyan Liang:** Formal analysis, Investigation, Supervision, Writing – review & editing. **Yan Zhang:** Data curation, Investigation, Writing – review & editing. **Ding Yuan:** Investigation, Writing – review & editing. **Tongwen Sun:** Conceptualization, Supervision, Writing – review & editing. **Yi Li:** Conceptualization, Writing – review & editing. **Yanxia Gao:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Supervision, Writing – review & editing.

## Data availability

The data and materials are available from the corresponding author upon reasonable request.

## Declaration of competing interest

All authors have no conflicts to disclose.

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Not applicable.

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