Holistic review and meta-analysis of independent impact of the residual SYNTAX score on prognosis in patients with acute coronary syndrome

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ABSTRACT

Objectives. The appropriate extent of revascularization following primary intervention is unknown. We conducted a systematic review and meta-analysis of residual Syntax score (rSS) to predict the outcomes and provide guide to optimal management of revascularization following primary intervention. Design. Previously published studies from 2007 to 2020 assessing the prognostic impact of rSS after ACS were included for this meta-analysis. The primary endpoint was defined as the major adverse clinical events (MACE) in multivariable analysis. The risk ratios (RRs) with 95% confidence intervals (CI) were calculated using the RevMan 5.4 software. Results. A total of 8,157 participants complicated with ACS from 12 clinical studies were included in this analysis. Based on the wide range of rSS studies available, we classified it into two major groups: rSS < 8 and rSS ≥ 8. In multivariate analysis, the rSS was an independent risk marker for MACE along with all-cause mortality, cardiovascular mortality, and recurrent myocardial infarction without significant heterogeneity [RR = 1.60 (1.03–1.07), 2.30 (1.57–3.38), 3.57 (2.09–6.10) and 1.70 (1.38–2.09), respectively]. The patients with rSS ≥ 8 presented higher frequency of all-cause mortality [RR = 2.99 (2.18–4.09)], cardiovascular death [RR = 3.32 (2.22–4.95)], and recurrent myocardial infarction [RR = 1.64 (1.34–2.02)]. Conclusion. The meta-analysis indicated that an rSS value of 8 could be a reasonable cut-off for incomplete revascularization after ACS and is an efficient tool to guide revascularization. In future, detailed research should focus on investigation of the optimal value of the rSS score.

1. Introduction

Among the patients suffering with acute coronary disease, approximately 50% of them presented with multivessel coronary disease in clinical practice. According to the current recommended guidelines, the optimal strategy is to achieve recovery of the flow and revascularization of culprit vessels as soon as possible during emergency. Although culprit lesions contribute to worsening of prognosis in acute phase [1], the serious residual nonculprit lesions in the coronary have equivalent in the risk of recurring incidence or further complications like myocardial ischemia and impairment of the long-term outcomes. Hence, series of studies have recommended that complete revascularization (CR) is superior to incomplete revascularization (ICR) regarding prognosis following PCI [2,3]. However, CR is scarcely performed on patients with complex and diffuse lesions. Recent studies [4,5] demonstrate that it’s acceptable to conduct reasonable incomplete revascularization (RICR) which could be an alternative for CR without affecting outcome.

The SYNTAX (Synergy Between PCI With Taxus and CABG) score is considered as an efficient tool guiding to assess the severity of coronary disease and select eligible people for PCI or CABG based on the anatomical features of coronary lesions. The residual SYNTAX score(rSS) is a quantitative measure of the complexity and degree of residual coronary artery lesions after percutaneous coronary intervention (PCI). Most importantly, this auxiliary score has been validated as an independent predictor of worse clinical outcomes among diverse population [6–8]. Furthermore, the link between the rSS and worse prognosis in patients with ACS has also been established by previous studies in details [7,9–11]. However, the optimal cut-off value of rSS which refers as reason incomplete revascularization regarding prediction of prognosis remains controversial. Therefore, we performed a systematic review and meta-analysis to elucidate the impact of rSS on prognosis of ACS patients following PCI. Finally, our estimates of the extent to which the reasonable ICR is appropriate will be
determined by rSS in accordance with the current evidence supported by published papers.

2. Methods and materials

2.1. Data sources and search strategy

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Pubmed, Embase, and Cochrane Database of systematic reviews were searched from beginning till October 2020, using a combination of the following terms:

1. Residual SYNTAX Score
2. Residual SYNTAX Score and percutaneous coronary intervention
3. Residual SYNTAX Score and intervention cardiology
4. Residual SYNTAX Score and coronary angioplasty
5. Residual SYNTAX Score and acute coronary syndrome
6. Residual SYNTAX Score and ST segment elevation myocardial infarction
7. Residual SYNTAX Score and Non-ST segment elevation myocardial infarction
8. Residual SYNTAX Score and Unstable Anginas

Our search strategy involved publications in English language and human patients.

2.2. Selection criteria for inclusion and exclusion of data

The inclusion criteria used for this study was defined as: (1) the data obtained was randomized and observational ones of patients which suffering with ACS and undergoing PCI; (2) The patients were evaluated and categorized by residual SYNTAX Score following PCI; (3) The major adverse clinical events (MACE) were assessed using the available data. The exclusion criteria was set as below: (1) the meta-analysis, reviews, case studies, letters to editor or conference abstract were not involved; (2) the residual SYNTAX Score was not performed to assess the patients; (3) the studies that could not provide relevant data that was available to this meta-analysis; (4) any duplications or overlapping or derived studies were excluded; (5) the studies which did not report adverse clinical outcomes including all-cause or cardiovascular death, recurrent myocardial infarction, revascularization, and ischemia stroke; (6) non-published data were excluded too.

2.3. Outcome selection and follow-up time

The primary endpoint was the analysis of impact of rSS on major adverse clinical events by pooling with logarithmic transformation results of multivariable adjusted estimates from the included studies.

The secondary endpoints were as following: (1) the impact of rSS on all-cause and cardiovascular mortality at multivariable and univariate analysis; (2) the impact of rSS on MACE at univariate analysis; (3) the impact of rSS on recurrent myocardial infarction, revascularization, and ischemia stroke at univariate analysis. Among 11 articles included, Diez-Delhoyo et al. (2016) [12], Song Ying et al. (2017) [13] didn’t mention when rSS was calculated, Yash Singbal et al. (2017) [7], ACUTY study (2016) [14] accessed rSS after culprit-lesion PCI, other studies [9,11,15-19] calculated rSS after staged PCI.

2.4. Data extraction and quality assessment

All data were obtained from articles published in peer reviewed journals and curated databases. The three authors (J.Y, D.F. and C.L.) independently extracted the data from the eligible studies for this analysis. The following relevant information were included: (1) name of first author; (2) year of published paper; (3) E-mail address of correspondence; (4) type of eligible studies; (5) type of enrolled participants; (6) baseline of characteristics of the participants (including average age, percentage of gender of participants, percentage of participants presented with hypertension, hyperlipidemia, diabetes mellitus, and smoking); (7) the number of participants in different rSS group; (8) the definition and prevalence of MACE reported by the studies; (9) the follow-up periods; (10) detailed information about quality of the studies; (11) location; (12) the confounder factor at multivariable analysis.

Similarly, the three authors assessed the quality of the studies involved by Newcastle Ottawa Scale (NOS) [20] respectively. The maximum total number of 9 stars implied as highest methodological quality from 8 components. The stars given to each component as follows: Representativeness of the Exposed Cohort *; Selection of the Non-Exposed Cohort *; Ascertainment of Exposure *; Demonstration That Outcome of Interest Was Not Present at Start of Study *; Comparability of Cohorts on the Basis of the Design or Analysis **; Assessment of Outcome *; Was Follow-Up Long Enough for Outcomes to Occur *; Adequacy of Follow Up of Cohorts *. Take PROSPECT study [18] earned 7 stars as example: Representativeness of the Exposed Cohort **; Selection of the Non-Exposed Cohort*; Comparability of Cohorts on the Basis of the Design or Analysis*; Assessment of Outcome*; Was Follow-Up Long Enough for Outcomes to Occur*; Adequacy of Follow Up of Cohorts*.

2.5. Data synthesis and analysis

Statistical data were pooled together in accordance with random-effects models or fixed-effect models using Review Manager 5 Software (Version 5.4, the Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark). A pooled analysis of adjusted odds ratio, relative ratio or hazard ratio were also performed after logarithmic transformation. Outcomes were reported as relative ratios (RR) and 95% confidence intervals (CIs) as the relative measure of association. Statistical heterogeneity across the studies was evaluated using the “I²” statistic to quantify

Determined by rSS in accordance with the current evidence supported by published papers.

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“inconsistency” among studies. $I^2$ values of 25% or less, 25–50%, and 50% or more used to represent low, moderate, and high level of inconsistency, respectively. Data were pooled using random-effects model for the anticipated high heterogeneity and using fixed-effect model for the low, moderate heterogeneity among studies. Sensitive analyses were planned for studies with low risk of biasness, studies with sample size over 10,000, using fixed-effects model to pool data or excluding the studies one by one. The publication bias was performed by visual inspection of funnel plots, and the asymmetry of the funnel plot was evaluated via Egger’s tests. All tests were two-sided and statistical significance was defined as $p < 0.05$. We used Chi-square ($\chi^2$) test or t-test appropriately to compare the proportions of prognostic factors.

3. Results
3.1. Search outcomes and study screen

Our search strategy yielded 3,265 publications from various public domain electronic databases. After initial screening by title and abstract, 41 studies were found to eligible for review and after full examination of these research articles a total of 3,224 publications were excluded. Details of excluded studies are provided in Figure 1. In brief, 19 studies were excluded due to conference abstract and 7 studies failed to gain the full paper from authors. 2 studies were removed due to overlapping data while another 2 studies did not fulfill the above included criteria. Finally, 11 studies with 7,853 patients met our eligibility criterion set for this systematic review. The region wise distribution of these studies was like, three studies were from Asia, three from Europe, two from North America, two from Australia and one from Africa.

The summary and general features of the studies are listed in Tables 1 and 2. The eleven studies were cohort studies. The average follow-up duration for ACS patients was of 12 months in ten studies, except one study reported 6 months as follow-up period [12]. Nine of the studies reported the prevalence of MACE as primary endpoints, except for two ones [7,12]. As different studies identified different range of residual SYNTAX score, we further classified these scores into two different groups: CR versus ICR, and rSS $< 8$ versus rSS $\geq 8$. After the quality assessment, the score of 7–8 from four studies present high quality whereas the allotted star ranged from 4 to 6 stars (Table 2).

![Figure 1. Schematic diagram of data screening (or flow chart of the data screening).]
Next, baseline characteristics of all studies are demonstrated on Table 3. The demographic baseline of two studies [9,21] were found to be missing. For other studies, enrolled patients had an average age of 60 years and were predominantly of male gender. In the lower rSS group, the proportion of patients with hypertension or diabetes mellitus was relatively lower whereas was not the same finding in prevalence of smoking and hyperlipidemia.

### 3.2. Impact of residual syntax score at multivariable analysis

Six studies reported a relative ratio (RR) of residual Syntax score as a continuous variable on MACE after adjustment for confounders were included at multivariate analysis. As presented in Figure 2, patients with rSS > 0 had higher risk of MACE [RR: 1.03, 95% confidence interval (CI): 1.00–1.08, \( p = .08 \)] with high heterogeneity (\( I^2 = 69.9\% \)). The results from logarithmic transformation showed that rSS is an independent factor for all-cause and cardiovascular mortality (RR: 1.05, 95% CI: 1.03–1.07, \( p < .001 \) and 1.06, 95% CI: 1.04–1.08, \( p < .001 \), respectively) with no heterogeneity.

### 3.3. Impact of incomplete revascularization on prognosis

After pooling all the data from seven studies (Figure 3), the presence of ICR could not only adversely impact on MACE...
3.4. Impact of rSS ≥ 8 on prognosis

Patients with rSS ≥ 8 showed (Figure 4) higher prevalence of MACE (RR: 1.79, 95% CI: 1.40–2.30, p < .001) and mortality (all-cause: 2.99, 95% CI: 2.18–4.09, p < .001; cardiovascular: 3.32, 95% CI: 2.22–4.95, p < .001) and recurrent myocardial infarction (RR: 1.64, 95% CI: 1.34–2.02, p < .001). It should be noted that, there was no heterogeneity on all-cause mortality and myocardial infarction. The occurrence of revascularization was higher in patients with rSS ≥ 8 (RR: 1.69, 95% CI: 1.18–2.40, p < .005), moreover these patients represented highly significant level of heterogeneity.

3.5. Sensitivity analysis and publication biasness

The sensitivity analysis was conducted by excluding the single studies one by one. When excluding the PROSPECT study [18] in terms of cardiovascular death, the statistical heterogeneity was reduced from 43% to 9% (RR: 4.32, 95% CI: 2.37–7.90, p < .001) in CR vs. ICR group, while from 36% to 0% (RR: 3.76, 95% CI: 2.46–5.73, p < .001) in rSS ≥ 8 vs. rSS < 8 group (shown in Supplementary Figures 1 and 2). Moreover, the statistical heterogeneity was eliminated (shown Supplementary Figure 3) by exclusion of the study of Sonya et al. [22] in terms of recurrent MI when comparing CR group with ICR group (RR: 1.51, 95% CI: 1.21–1.87, p < .001). Further, we observed removal of any other single study, did not had any obvious effect on statistical heterogeneity. Moreover, the sensitivity analyses did not reveal any significant deviation from the main result of this analysis. All the clinical endpoints were assessed via the visual inspection of funnel plots (Figure 5). There has been some evidence for the existence of publication bias among all the studies.

4. Discussion

In the present study, we investigated the impact of residual SYNTAX score on prognosis and mortality at multivariate and univariate analysis. The results of the pooled data from different studies indicated that (1) ACS patients receiving complete revascularization have advantage over all-cause and cardiovascular mortality and recurrent myocardial infarction compared with the ones with incomplete
revascularization; (2) an rSS could be an independent risk marker for adverse clinical events, particularly for all-cause and cardiovascular mortality after adjusting the cofound risk factors; (3) PCI with an rSS less than 8 could reduce the risk of MACE

Derived from SYNTAX score, residual SYNTAX score was firstly proposed by Généreux et al. [10] in a sub-study of ACUITY. An rSS was used to quantify and risk-stratify the angiographic completeness of revascularization after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) similarly to or better than bSS [23]. In this present study, rSS was a strong independent predictor of mortality and all ischemic outcomes for ACS patients in the multivariate analysis. A series of studies have provided adequate evidence that low rSS is associated with improved clinical outcomes [6,23–25]. Theoretically, the residual SYNTAX score would be impacted by the fallacies which inherited from the SYNTAX score, including conflicting reports on its efficacies of predicting outcomes [26,27], failures in reflecting the variability in the coronary trees [28,29], and arbitrary point assignment for those adverse characteristics defined in the SYNTAX score [30]. Hence, it still remains controversial regarding association between rSS and MACE or mortality after presenting with an ACS [12,19]. Complete revascularization, assessed by the rSS value of 0, was achieved from 15.1% up to 41.8% patients with ACS [10,13,17–19,31]. It was still superior to incomplete revascularization with regards to MACE and death following adjustment of confounder factors. It is of interest to note that patients without rSS could drop off the 60% of MACE at univariate analysis. Moreover, even significant reductions in both, all-cause and cardiovascular death were observed. Accordingly, rSS is associated with mortality and could be an efficient tool to gauge the severity and extensity of the remaining disease burden.

Vessel complexity and clinical status of patient’s health (chronic total occlusions, calcified lesions, acute decompensated heart failure, or respiratory failure, etc.) may contribute to incomplete revascularization. Although, the complete revascularization is an ideal target in the setting of ACS and progressively performed by advanced techniques; patients with incomplete revascularization can be accounted for at least 30% in clinical practice [23,32,33]. The rational management and intervention strategy of complex multivessel disease remained a major challenge for operators. Based on the results from the optical coherence tomography sub-study of the COMPLETE [34], the unstable obstructive non-culprit disease generally results in subsequent risk in the course of primary PCI. According to the study of Sony et al. [23], reasonable incomplete revascularization was defined as the rSS value of less than 8 and achieved similar incidence of clinical outcome compared with complete
revascularization. With respect to age factor, the older patients likely to have diabetes, lower left ventricle ejection fraction, more complex coronary disease or clinical comorbidity, reasonable incomplete revascularization is a significant indication for the operator and is of great necessity. When Généreux et al. [10] proposed residual SYNTAX score, they described the data-based result that patients with rSS > 8 tend to have an increased risk on prognosis within first year. In the study of Farooq et al. [2], the patients were divided into 4 groups according to the rSS values, the group

Figure 3. Forest plot of MACE, all-cause mortality, cardiovascular mortality, myocardial infarction, and revascularization in ACS patients with ICR vs. CR (ICR-incomplete revascularization; CR-revascularization).

| Study or Subgroup | CR Events | Total Events | CR Risk Ratio | M-H Fixed, 95% CI |
|------------------|-----------|--------------|---------------|-------------------|
| ACUITY study 2016 | 31 1602 15 1084 21.5% | 1.29 [1.08, 1.51] | 2012 |
| PROSPECT study 2019 | 103 504 28 184 17.8% | 1.34 [1.02, 1.79] | 2014 |
| Song, Ying 2017 | 153 823 60 591 21.1% | 1.82 [1.38, 2.42] | 2017 |
| Sonya N Burgess 2018 | 35 343 2 150 3.2% | 7.63 [3.16, 19.8] | 2018 |
| Yutaka Kikuchi 2018 | 58 484 11 83 11.6% | 0.94 [0.52, 1.72] | 2019 |
| Attia Öskan 2018 | 32 30 10 78 9.2% | 5.00 [1.12, 22.4] | 2019 |
| Yaping Zeng 2019 | 60 529 12 224 11.6% | 0.11 [0.11, 1.98] | 2019 |
| Total (95% CI) | 4394 2394 100% | 1.60 [1.22, 2.09] | 2019 |
| Heterogeneity: Tau² = 0.37, Chi² = 15.97, df = 6 (P = 0.06); I² = 62% |
| Test for overall effect: Z = 3.44 (P = 0.0008) |

| (b) All-cause mortality |
|------------------------|
| Study or Subgroup | CR Events | Total Events | CR Risk Ratio | M-H Fixed, 95% CI |
| ACUITY study 2016 | 40 1502 15 1084 43.0% | 2.17 [1.21, 3.90] | 2014 |
| Attia Öskan 2018 | 10 130 2 78 6.1% | 3.02 [0.67, 1.34] | 2017 |
| Song, Ying 2017 | 20 823 7 591 9.9% | 0.05 [0.87, 4.82] | 2017 |
| Sonya N Burgess 2018 | 54 439 6 150 21.3% | 3.08 [0.15, 7.00] | 2018 |
| Yutaka Kikuchi 2018 | 12 109 2 83 9.3% | 0.17 [0.24, 4.7] | 2018 |
| Total (95% CI) | 3458 1906 100% | 2.30 [1.57, 3.38] | 2018 |
| Heterogeneity: Chi² = 1.73, df = 4 (P = 0.78); I² = 0% |
| Test for overall effect: Z = 4.27 (P < 0.0001) |

| (c) Cardiovascular death |
|--------------------------|
| Study or Subgroup | CR Events | Total Events | CR Risk Ratio | M-H Fixed, 95% CI |
| ACUITY study 2016 | 31 1502 4 1084 24.8% | 5.24 [1.88, 14.1] | 2014 |
| PROSPECT study 2019 | 9 504 3 184 22.8% | 0.97 [0.26, 3.83] | 2015 |
| Song, Ying 2017 | 18 823 4 591 24.0% | 3.23 [0.10, 9.50] | 2017 |
| Sonya N Burgess 2018 | 35 343 2 150 14.3% | 7.63 [1.86, 34.1] | 2018 |
| Yaping Zeng 2019 | 6 529 2 224 14.5% | 1.27 [0.26, 6.26] | 2019 |
| Total (95% CI) | 3800 2233 100% | 3.57 [2.09, 6.19] | 2019 |
| Heterogeneity: Chi² = 7.03, df = 4 (P = 0.13); I² = 43% |
| Test for overall effect: Z = 4.65 (P < 0.0001) |

| (d) Myocardial infarction |
|---------------------------|
| Study or Subgroup | CR Events | Total Events | CR Risk Ratio | M-H Fixed, 95% CI |
| ACUITY study 2016 | 169 1502 75 1084 64.2% | 1.52 [1.17, 1.97] | 2016 |
| PROSPECT study 2019 | 13 504 3 184 22.8% | 0.98 [0.27, 3.67] | 2019 |
| Song, Ying 2017 | 23 823 11 591 9.2% | 1.50 [0.85, 2.14] | 2017 |
| Sonya N Burgess 2018 | 80 343 7 150 7.0% | 4.25 [0.00, 9.03] | 2018 |
| Yaping Zeng 2019 | 9 529 2 224 2.0% | 1.70 [0.36, 7.93] | 2019 |
| Yutaka Kikuchi 2018 | 27 109 4 83 4.9% | 1.07 [0.13, 8.3] | 2019 |
| Total (95% CI) | 4394 2394 100% | 1.70 [1.38, 2.09] | 2019 |
| Heterogeneity: Chi² = 11.44, df = 5 (P = 0.00); I² = 46% |
| Test for overall effect: Z = 4.97 (P < 0.0001) |

| (e) Revascularization |
|----------------------|
| Study or Subgroup | CR Events | Total Events | CR Risk Ratio | M-H Random, 95% CI |
| ACUITY study 2016 | 188 1502 109 1084 25.3% | 1.17 [0.93, 1.49] | 2016 |
| PROSPECT study 2019 | 86 504 24 184 29.1% | 1.31 [0.86, 1.99] | 2019 |
| Song, Ying 2017 | 106 823 43 591 22.4% | 1.77 [1.26, 2.48] | 2017 |
| Sonya N Burgess 2018 | 80 343 10 150 14.9% | 4.50 [1.67, 12.5] | 2018 |
| Yaping Zeng 2019 | 26 529 0 224 1.5% | 22.54 [1.38, 368.3] | 2019 |
| Yutaka Kikuchi 2018 | 32 464 5 83 9.8% | 1.14 [0.46, 2.85] | 2019 |
| Total (95% CI) | 4394 2394 100% | 1.65 [1.16, 2.36] | 2019 |
| Heterogeneity: Tau² = 0.12, Chi² = 17.40, df = 6 (P = 0.008); I² = 86% |
| Test for overall effect: Z = 2.79 (P < 0.005) |
of rSS > 8 was highly associated with all-cause mortality and MACE at 5-years in comparison with other groups. As our study presented, our meta-analysis pooled 6 studies indicated that ACS patients with rSS/C21 > 8 had a 79% higher risk to MACE. Regarding all-cause and cardiovascular death and recurrent myocardial infarction, the increment of risk reaches twice time than the one with rSS < 8. Altogether, the value rSS of 8 could be a vital mark in degree of revascularization and a line of demarcation for clinical prognosis following primary PCI. The rSS system could classify the

### Figure 4.
Forest plot regarding MACE, all-cause mortality, cardiovascular mortality, myocardial infarction, and revascularization in ACS patients with rSS < 8 vs. rSS ≥ 8. (ICR: incomplete revascularization; CR: revascularization).

| Study or Subgroup | rSS>8 | rSS=8 | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-------------------------------|-------------------------------|
| **(a) MACE**      | Events | Total | Weight | Events | Total | Weight |
| ACUITY study 2016 | 110    | 501   | 372   | 2195  | 24.9%  | 1.29 [1.07, 1.58] |
| Dezie-Delhroyo 2018 | 40  | 55  | 3  | 21  | 4.6%  | 5.09 [1.76, 14.70] |
| Mohamed Loubfi 2015 | 11 | 36  | 9  | 94  | 7.4%  | 2.85 [1.29, 6.28] |
| PROSPECT study 2019 | 38 | 140 | 85 | 594 | 16.8% | 1.56 [1.13, 2.21] |
| Song, Ying 2017 | 86 | 294 | 147 | 1120 | 21.8% | 1.71 [1.32, 2.22] |
| Sonya N Burgess 2018 | 89 | 193 | 88 | 396 | 22.7% | 2.08 [1.63, 2.64] |
| **Total (95% CI)** | 1219 | 4390 | 100.0% | 1.79 [1.40, 2.30] |
| **Total events** | 352 | 714 |
| Heterogeneity: Tau² = 0.06; Chi² = 18.33, df = 5 (P = 0.006), I² = 69% |
| Test for overall effect: Z = 4.59 (P < 0.00001) |

| **(b) All-cause mortality** |
|-----------------------------|
| Study or Subgroup | rSS>8 | rSS=8 | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-------------------------------|-------------------------------|
| ACUITY study 2016 | 23 | 501 | 41 | 2185 | 39.4% | 2.45 [1.48, 4.04] |
| Dezie-Delhroyo 2018 | 14 | 55  | 0  | 21  | 3.7%  | 6.02 [3.12, 11.64] |
| Mohamed Loubfi 2015 | 2 | 36  | 1  | 64  | 1.5%  | 4.87 [0.44, 49.93] |
| Song, Ying 2017 | 13 | 294 | 14 | 1120 | 15.0% | 3.54 [1.68, 7.44] |
| Sonya N Burgess 2018 | 35 | 193 | 25 | 396 | 42.2% | 2.87 [1.77, 4.68] |
| **Total (95% CI)** | 1079 | 3806 | 100.0% | 2.99 [2.18, 4.60] |
| **Total events** | 87 | 81 |
| Heterogeneity: Chi² = 1.87, df = 4 (P = 0.78), I² = 0% |
| Test for overall effect: Z = 6.63 (P < 0.00001) |

| **(c) Cardiovascular death** |
|-----------------------------|
| Study or Subgroup | rSS>8 | rSS=8 | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-------------------------------|-------------------------------|
| ACUITY study 2016 | 13 | 501 | 22 | 2185 | 36.6% | 2.58 [1.31, 5.08] |
| Dezie-Delhroyo 2018 | 2 | 140 | 9 | 594 | 15.5% | 0.93 [0.20, 4.24] |
| Mohamed Loubfi 2015 | 12 | 294 | 10 | 1120 | 18.6% | 4.57 [1.39, 10.48] |
| Sonya N Burgess 2018 | 23 | 193 | 10 | 396 | 28.3% | 4.72 [2.29, 9.72] |
| **Total (95% CI)** | 1128 | 4285 | 100.0% | 3.32 [2.22, 4.95] |
| **Total events** | 50 | 51 |
| Heterogeneity: Chi² = 4.72, df = 3 (P = 0.119), I² = 36% |
| Test for overall effect: Z = 2.50 (P < 0.00001) |

| **(d) Myocardial infarction** |
|-----------------------------|
| Study or Subgroup | rSS>8 | rSS=8 | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-------------------------------|-------------------------------|
| ACUITY study 2016 | 58 | 501 | 184 | 2185 | 58.9% | 1.40 [1.08, 1.84] |
| Dezie-Delhroyo 2016 | 26 | 55  | 3  | 21  | 3.7%  | 3.31 [1.12, 9.79] |
| Mohamed Loubfi 2015 | 3 | 36  | 4  | 84  | 2.1%  | 1.75 [0.41, 7.42] |
| PROSPECT study 2019 | 6 | 140 | 14 | 594 | 4.6%  | 1.79 [0.70, 4.57] |
| Song, Ying 2017 | 11 | 294 | 26 | 1120 | 9.3%  | 1.81 [0.81, 3.22] |
| Sonya N Burgess 2018 | 37 | 193 | 38 | 396 | 21.4% | 2.00 [1.31, 3.04] |
| **Total (95% CI)** | 1219 | 4390 | 100.0% | 1.64 [1.34, 2.02] |
| **Total events** | 142 | 269 |
| Heterogeneity: Chi² = 3.79, df = 5 (P = 0.59), I² = 0% |
| Test for overall effect: Z = 4.71 (P < 0.00001) |

| **(e) Revascularization** |
|-----------------------------|
| Study or Subgroup | rSS>8 | rSS=8 | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------|-------|-------------------------------|-------------------------------|
| ACUITY study 2016 | 83 | 501 | 234 | 2185 | 27.5% | 1.17 [0.80, 1.53] |
| Dezie-Delhroyo 2016 | 9  | 36  | 4  | 84  | Not estimable | |
| PROSPECT study 2019 | 31 | 140 | 79 | 594 | 23.9% | 1.84 [1.13, 2.37] |
| Song, Ying 2017 | 44 | 294 | 105 | 1120 | 25.3% | 1.60 [1.15, 2.22] |
| Sonya N Burgess 2018 | 52 | 193 | 30 | 396 | 23.5% | 2.01 [1.52, 4.11] |
| **Total (95% CI)** | 1128 | 4285 | 100.0% | 1.69 [1.18, 2.40] |
| **Total events** | 180 | 456 |
| Heterogeneity: Tau² = 0.10, Chi² = 13.76, df = 3 (P = 0.003), I² = 78% |
| Test for overall effect: Z = 2.89 (P = 0.004) |
risk stratification for patients with multivessel disease and help to guide for subsequent intervention strategy.

In this study, some moderate heterogeneity remained among different study. Data from the prospective trial and Yuhei’s study, there is a lower frequency of cardiovascular death. As presented the sensitivity analysis, moderate heterogeneity was eliminated by concealing those data. In those two studies, it was noting that combing IVUS or FFR into rSS may better predict the future non-culprit-related events and subsequently cut down the prevalence of mortality compared with the ones which were guided by angiography [18,19]. In recent studies, it has been reported that morphological or physiological assessment by IVUS or FFR may contribute to better prediction of high-risk patients compared with angiographic assessment alone [35,36]. Moreover, calculation of rSS was based on angiography after the PCI procedure and has been reported to have moderate interobserver variability [37]. Patients with extensive unrevascularized territories or small amounts of residual ischemic myocardium may be involved together and further contributed to conflicting results.

5. Limitations of the study
Some limitations should be cautioned in this study. First, the number of patients with CR were relatively smaller while the ratio of complete revascularization was up to 60% in recent studies. Still, the rSS proved to be a practical

Figure 5. Funnel plot (a) and (b) representing publication bias regarding ACS patients with ICR vs. CR and with rSS < 8 vs. rSS ≥ 8, respectively.
evaluation tool for coronary anatomy and was associated with cardiac and all-cause mortality, and recurrent myocardial infarction. Next, both prospective and retrospective studies were included and can introduce a potential bias into the study. The sub-group analysis indicated that prospective study might account for the heterogeneity. On the other hand, the rSS has the same defects inherited from SYNTAX score, such as inconsistent prediction [26,27], an overestimate for the adverse characters of patients undergone CABG [30], several limitations in reflecting the variable form of the coronary tree [28]. Hence, the large-scale randomized trial regarding the impact of rSS on clinical outcomes is of necessity further. Moreover, given the inaccessible raw data of trails included, the pooled and detailed subgroup analysis wasn’t conducted which influence the quality and heterogeneity of this study. Finally, the definition of MACE among these studies varied slightly. All this could contribute to some heterogeneity among variety of studies analyzed here.

6. Conclusion

Our study reveals that higher rSS value is related to increased risk in mortality among ACS patients. As complete revascularization could be difficult to achieve in all clinical cases, reasonable incomplete revascularization defined as rSS < 8 will be a helpful measure to predict prognosis and serve as a guiding tool for the management of revascularization operation. Further, detailed investigations on this matter could help to determine an optimum value of this score.

Disclosure statement

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