Peer Review Report

Review Report on Risk prediction for sudden cardiac death in the general population: a systematic review and meta-analysis

Original Article, Int J Public Health

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EVALUATION

Q 1 **Please summarize the main findings of the study.**

The present systematic review and meta-analysis synthesizes the current state of the literature on the prediction of sudden cardiac death in the general population. Through an extensive literature search, the authors identified 15 studies that analyzed sociodemographic, clinical, laboratory, electrocardiographic, and echocardiographic factors as predictors of sudden cardiac death in this population. Unfortunately, the meta-analyses performed could only include 2 studies each due to the heterogeneity of the included studies. The authors highlight four potential variables as predictors of this outcome: diagnosis of diabetes mellitus, QRS duration, spatial WRS-T angle, and fractional shortening. On the other hand, they highlight the existence of studies only in the United States and Europe.

Q 2 **Please highlight the limitations and strengths.**

The authors addressed a topic relevant to clinical practice through a comprehensive review of the literature following the PRISMA statement recommendations, which allowed the characterization of the current evidence on factors associated with SCD in detail. Likewise, the meta-analysis identified those factors whose association with the outcome of SCD is potentially consistent across studies. Finally, the discussion addresses in detail some of the most relevant factors of interest for daily clinical practice.

On the other hand, I have highlighted some limitations in my comments that merit changes in different sections of the article, highlighting the pooling of effect measures, the potential variability in the definitions of SCD, as well as the need for additional characterization of relevant factors not included in the meta-analysis, among others.

Q 3 **Please provide your detailed review report to the authors. The editors prefer to receive your review structured in major and minor comments. Please consider in your review the methods (statistical methods valid and correctly applied (e.g. sample size, choice of test), is the study replicable based on the method description?), results, data interpretation and references. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

In general, the design and writing of the study are adequate, and the conclusions are in line with the results. However, there are some relevant points that deserve discussion.

Major comments:
-The authors mention that they considered hazard ratios (HR) and risk ratios (RR) as equivalent measures of effect. As almost all studies used Cox proportional hazards models, it is not clear in which of them RR were extracted/used, or if the authors used RR at all. Considering that the methods section explicitly mentions this, I would like to comment on this. As the authors are aware, although both the HR and RR compare risks between groups, they do so in fundamentally different ways. The HR provides a ratio of instantaneous risks at a given point in time, whereas the RR provides a cumulative risk over a period. Therefore, RR will vary over the study period as they depend on survival and censoring at each specific time, with longer study durations leading to a convergence of relative risks, while HR will remain constant. On the other hand, only at very short (infinitesimal) times will HR and RR have a systematic relationship. This does not mean, in my opinion, that the

analysis would be completely wrong if RR were considered equivalent to HR, as I am aware of the limited availability of information and the usefulness of providing meta-analytic results for at least some of the candidates identified as predictors of SCD. Therefore, I recommend including this limitation in the limitations section of the study.

-Another relevant point to highlight corresponds to the definition of SCD used in the included studies, considering the variations in the definition and the different methodologies used in the studies to identify a case as SCD. It is relevant not only for the implications this has for the interpretation of the results, but also for the evaluation of the different variations in the definition of SCD in the literature in this context. Authors should include this definition/methodology of SCD used in each study in a supplementary table.

-On the other hand, although the meta-analytic approach allows us to identify factors whose measure/direction of effect is preserved or consistent in multiple studies and to increase the power to detect significant effects, the wide heterogeneity of the factors evaluated in the studies limits the possibility of this approach including predictors with high potential if they have been evaluated in a single study or were reported in a different way in two or more studies. Therefore, I consider it relevant to identify and mention those predictors that, although they were not included in the meta-analysis, have potential applicability for predicting sudden cardiac death due to factors such as considerable effect size, high sample size, and study quality, availability of the measurement in the population context, and high discrimination of the model or significant additive value when added to the model, among others. Another approach would be to mention the best-reported prediction model, mentioning the setting and the included variables.

Minor comments:
-Some inclusion and exclusion criteria correspond to the other's counterpart. I suggest leaving only one per pair.

- In the first paragraph of the results section, the information on study selection can be abbreviated, as this information is summarized in Figure 1.

- The availability of data to replicate analyses is a relevant measure of study quality. The authors should mention the proportion of studies that included a data availability statement and which of them allowed direct access to the study data.

- Although Table 1 provides valuable information on the included studies, relevant sociodemographic variables of the population are missing. Reporting the age and sex distribution of the individual populations may provide additional information relevant to the interpretation of the results.

Some typos/writing issues I identified:

-Line 65: “However, systematic reviews or meta-analyses did not explore predictors of SCD risk inadequately”

-Line 75: “We performed an electronic literature search of PubMed, Embase, Cochrane Library (including CENTRAL, NIH registry, and CTRI), Web of Science, CINAHL and OpenGrey databases with no date restrictions. Searches were performed in the following databases on March 1, 2023.”

-Line 254: It is displayed as = while it should be ≥.

-Line 314: “machine learning appears to suggest machine learning may have some incremental utility in predicting SCD”

-Line 332: “It was not being possible to assess the existence of publication bias”

-Figure 2: Tamariz L C Statistic information of the SCD score unavailable. 95% Confidence Intervals of the C Statistic for some studies are not reported.

PLEASE COMMENT

Q 4 Is the title appropriate, concise, attractive?

Yes.

Q 5 Are the keywords appropriate?

Yes.

Q 6 Is the English language of sufficient quality?

There are some issues that merit review.

Q 7 Is the quality of the figures and tables satisfactory?

Yes.

Q 8 Does the reference list cover the relevant literature adequately and in an unbiased manner?)

Yes.

QUALITY ASSESSMENT

Q 9	Originality	■■■□□
Q 10	Rigor	■■■□□
Q 11	Significance to the field	■■■■□
Q 12	Interest to a general audience	■■■□□
Q 13	Quality of the writing	■■■□□
Q 14	Overall scientific quality of the study	■■■□□

REVISION LEVEL

Q 15 Please make a recommendation based on your comments:

Major revisions.