INPLASY

Role of Non-invasive Heart Signals and Cancer Survival Characteristics- An Updated Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support is obtained.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - This study is the part of MSC (epidemiology) project, London School of Hygiene & Tropical Medicine, UK. This is being conducted as two parallel platforms, one sole by corresponding author under the supervision as a part of the MSC project, and other as a standard team for conducting the systematic review.

INPLASY registration number: INPLASY202370111

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2023 and was last updated on 8 March 2023.

INTRODUCTION

*R*eview question / Objective Whether noninvasive heart signals (heart rate variability indices) can predict the survival in patients with cancer?

Rationale Cancer is the leading cause of morbidity and mortality globally. The recurrence and metastatic spread are two key challenges in the cancer management. Majority of research is limited to pathological, surgical, and oncological management of such patients. In the context of oncological research, the role of non-invasive heart signals such as heart rate variability (HRV) has been the newer area of interest. Its role in prognostication and overall well-being is addressed in few studies. Only two systematic reviews (Zhou et al. 2016 and Kloter et al. 2018) exploring on prognostication role of HRV on cancer progression and survival are published. These reviews are based on searches from 2-3 databases only, and incorporated studies till 2016. Majority of included studies are retrospective in nature. In addition, 2016 meta-analysis did not mention about adjusted effect sizes (effects of modifiers or confounders), thus limits the validity of findings. Authors of other systematic review (Kloter et al. 2018) did not perform the quantitative meta-analysis and lacks focused primary outcome. Therefore, this updated systematic review and meta-analysis is an attempt to fill the gap in comprehensive understanding between HRV prognostication and cancer survival characteristics.

Condition being studied In the context of oncological research, the role of non-invasive heart signals such as heart rate variability (HRV) has

been the newer area of interest. This study is conducted for patients with cancer.

METHODS

Search strategy Key concepts- There are three main concepts: Heart rate variability, Cancer, and Prognosis.
Search terms/keywords/subject headings related to these three concepts- Term 1, 2 and 3 will be utilized in various combinations.
Term 1- Neoplasm, Neoplasia, Cancer, Cancers, Malignant, Malignancy, Malignancies, Benign, Benign Neoplasm, Tumors,
Term 2-HRV, heart rate variability, vagal tone, Vagal activity,
Term 3- Prognosis, Progression free survival, mortality, morbidity, complications, dead, death.

Participant or population This will include cancer patients with all age group. No gender restriction will be applied.

Intervention Non-invasive heart signals monitoring (HRV-indices).

Comparator High HRV indices, if information is available in more than 50% of included articles (Low HRV indices vs. High HRV indices).

Study designs to be included Every study designs will be included. In addition, any correspondence, abstracts, conference proceedings, letters mentioning study details will be included.

Eligibility criteria Inclusion- 1. All types of cancer ; 2. All age group; 3. No language restriction; 4. No gender restriction. Exclusions- 1 - Animal studies; 2- Duplicate reports and 3. Case series, case reports.

Information sources Search Strategies (Electronic-searches)- The specific search strategy will be developed. Literature searches will be conducted from inception to July 2023, of the following databases:1. MEDLINE 2. Embase 3. CINAHL (Cumulative Index to Nursing & Allied HealthLiterature) 4. Web of Science 5. Scopus. 6. Cochrane Database 7. Clinicaltrial.Gov 8. Grey literature If any relevant information is missing, corresponding authors will be contacted. The reference lists from the retrieved studies will be manually searched for additional citations.

Main outcome(s) Primary outcome-Survival Outcome as defined by individual article (commonly time period between first HRV screening and death or last follow up or any-other end point highlighted by articles.

Additional outcome(s) secondary outcome-Progression characteristics (Progression-free-, recurrence-free-or disease-free survival).

Data management Initial title and abstract screening for eligibility will be performed by two independent reviewers. Full text for titles that passed the initial screening will be retrieved and screened for eligibility. Any disagreement in the initial or full-text eligibility review will be resolved by consensus or by consulting to third reviewer. We will extract study characteristics independently using a standard data collection form developed on excel sheet.

Quality assessment / Risk of bias analysis Cochrane bias assessment tool for RCTs and Newcastle Ottawa Scale will be utilized for non-RCTs./observational studies.

Strategy of data synthesis Data collection and management- A standardized form will be used for data extraction from the included studies. Each study's demographics and primary and secondary outcomes will be recorded and presented in tables to organize, summarize the information, and identify trends across the data. Data synthesis The number of papers included and excluded during the systematic review process will be clearly presented in a flowchart for clear transparency (PRISMA flowchart). Papers selected will be presented in a summary table. Limitations of the studies will be discussed in detail Analytical Plan- Where outcome data are of sufficient quality and participants, comparisons and outcomes are judged to be sufficiently like ensure an answer that is clinically meaningful, a meta-analysis will be performed. Meta-analysis will b e performed by STATA (17.0) or REVMAN.
Dichotomous and continuous outcome summary data from each individual study will be entered into Forest plots, relative risk ratios/Hazard ratios/Odds ratios (95% confidence interval) or mean difference (95% confidence interval) and heterogeneity (χ^2 and I^2) will be generated for the outcomes.

Subgroup analysis If complete information about these variables are available-
1.Age,
2. Sex
Any other potential modifier or confounders (therapy, co-morbidities) are available across more than 50% manuscripts.

Sensitivity analysis 1. Based on quality of studies (Low vs fair/good)
2. Based on Publication before or after 2016
Depending upon the information available after data extraction, other sensitivity analyses will be performed after discussing with reviewer team.

Language restriction 1. No ENGLISH language restriction will be applied. Google translate will be utilized for the translation and if information is not retrieval, corresponding authors will be contacted.

Country(ies) involved Canada.

Keywords Heart Rate Variability, Cancer, Progression, Survival, Prognosis.

Contributions of each author
Author 1 - Tumul Chowdhury. (Concept, design, proposal, data extraction, synthesis, analysis, interpretation, manuscript writing).
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Author 2 - Krisha Patel. (Data extraction, table preparation, manuscript writing).
Author 3 - Emad Al-Azazi. (Data analysis, synthesis and writing).
Author 4 - Bernard Rachet. (data interpretation, conflict resolution, manuscript writing)
Author 5-Marina Englesakis (Information Specialist). (Data search strategy and upload, data search methodology writing).
Author 6- Terry Cho (Data extraction, presentation, preparation of tables/graphs, bias assessment, certainty or level of evidence assessment, manuscript edits)
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