Research Protocol

White blood cell counts and cancer prognosis: an umbrella review and meta-analysis

* Study questions
  + What is the overall value of WBC count (total, differential and ratios) as predictors of cancer outcomes?
  + How strong is the evidence for cell ratios and leukocyte sub-population counts as prognostic markers? Which cancer diagnoses are clearly associated and which require further study?
  + Can we summarise and assess the current evidence? Are there important biases that need to be addressed? How consistent are previous studies?
* Study design
  + Umbrella systematic review and meta-analysis ([Ioannidis, 2009](#_ENREF_3))
* Background
  + Inflammation and inflammatory processes in the body coincide with a diagnosis of cancer, however it is not clear which markers of inflammation have a predictive quality for cancer outcomes. Elevated total WBC count, a marker of inflammation, has been linked to cancer mortality (Shankar et al. 2006) and several meta-analyses have explored the prognostic significance of different WBC ratios (NLR and PLR) to outcomes of specific cancer diagnoses. An umbrella review can be used to systematically assess the relationships between these indicators of inflammation and outcomes across a wide scope of different cancer diagnoses.
  + Preliminary search for an existing umbrella review on this topic did not yield any results.
* Objectives
  + To evaluate systematic reviews and meta-analyses on the association between total WBC counts, differential WBC counts and ratios with different cancer outcomes;
  + To evaluate systematic reviews and meta-analyses of observational studies that investigated associations of cell counts and ratios with outcomes (overall survival, disease-free survival, and progression-free survival) in different cancer diagnoses;
  + To summarise the outcomes associated with cell counts and ratios; determine the presence of literature biases and outcomes without these, and evaluate the consistency of inferences from the previous studies.
* Outcomes
  + Primary outcome: the association of total WBC counts to cancer outcomes;
  + Secondary outcomes: the association of differential WBC subsets with cancer outcomes;
  + Tertiary outcomes: the association of WBC ratios with cancer outcomes;
* Inclusion and exclusion criteria
  + Participants
    - Defined diagnosis of cancer
    - Patients with lung, prostate, breast, colorectal, pancreatic, or gastric cancer
      1. Among most common cancers (also bladder?)
    - Cancer outcomes associated with WBC counts
  + Study designs and quality criteria
    - Systematic reviews and meta-analysis assessing WBC counts and their association to cancer outcomes in humans;
    - Articles were excluded if they were not original contributions; if treatment was the exposure of interest; and those in which diagnosis of cancer, overall survival, disease-free survival, or progression-free survival were not the outcome of interest.
    - Selected studies were assessed using the ROBIS tool.
  + Covariates, effect modifiers, and confounders
    - We noted and recorded any possible covariates, effect modifiers, and confounders (age, gender, diagnosis, duration of follow-up, risk of bias, smoking status, co-morbidity, chronic disease, ethnicity, haematocrit level, BMI).
    - We listed known and potential confounders and assessed included studies for quality and bias according to these;
    - Consider weighting studies according to sample size for instance.
* Study selection
  + Data sources and limits
    - MEDLINE and EMBASE were searched through OVID with no prior date and up until \_\_\_\_\_; original observational investigations and trials in humans, English language and with full text availability were included.
    - Justify exclusions.
      1. Rarely need to search past 1990, few systematic reviews prior to 1990.
  + Search strategy
    - 1. Study selection was performed by one researcher and checked by two additional researchers according to above criteria. A log with reasons of excluded studies from the second stage onwards is available.
      2. Authors, institutions, and journals were not considered in study selection
      3. Searches were performed for terms appearing in the title, abstract or keywords using the details below. Two stages were performed for each source: first, articles were scanned for exclusion criteria appearing in titles; second, remaining articles were searched for inclusion and exclusion criteria abstracts and full texts.
      4. For MEDLINE, we derived a list of 6324 articles for further inspection and a final list of xxx were included.
         1. Used a search filter from BMJ to identify systematic reviews and meta-analyses.
      5. For EMBASE, we derived a list of 1510 articles for further inspection and a final list of xxx were included.
         1. Used a search filter from SIGN to identify systematic reviews and meta-analyses.
      6. Additionally, reference lists of relevant articles were manually searched for additional citations not included above.
    - Search details were:
      1. MEDLINE (6324 articles):

1

((white blood cell or WBC or neutrophil\* or lymphocyte\* or leukocyte\* or platelet\*) and (marker\* or count\* or ratio\* or level\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

441392

2

(NLR or PLR).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6201

3

exp Leukocyte Count/

90932

4

1 or 2 or 3

446103

5

exp Neoplasms/

3005710

6

(cancer or Neoplasm\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2901245

7

5 or 6

3401110

8

4 and 7

81920

9

(review or review,tutorial or review, academic).pt.

2300257

10

(medline or medlars or embase or pubmed or cochrane).tw,sh.

151292

11

(scisearch or psychinfo or psycinfo).tw,sh.

18611

12

(psychlit or psyclit).tw,sh.

941

13

cinahl.tw,sh.

17908

14

((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.

10398

15

(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.

24696

16

(pooling or pooled or mantel haenszel).tw,sh.

79819

17

(peto or dersimonian or der simonian or fixed effect).tw,sh.

5509

18

(retraction of publication or retracted publication).pt.

10592

19

9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

2426466

20

9 and 19

2300257

21

meta-analysis.pt.

80495

22

meta-analysis.sh.

80495

23

(meta-analys$ or meta analys$ or metaanalys$).tw,sh.

141215

24

(systematic$ adj5 review$).tw,sh.

115818

25

(systematic$ adj5 overview$).tw,sh.

1486

26

(quantitativ$ adj5 review$).tw,sh.

6208

27

(quantitativ$ adj5 overview$).tw,sh.

254

28

(quantitativ$ adj5 synthesis$).tw,sh.

1995

29

(methodologic$ adj5 review$).tw,sh.

4895

30

(methodologic$ adj5 overview$).tw,sh.

337

31

(integrative research review$ or research integration).tw.

121

32

21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

219343

33

20 or 32

2399734

34

8 and 33

6324

* + - 1. EMBASE (1510 articles):

1

((white blood cell or WBC or neutrophil\* or lymphocyte\* or leukocyte\* or platelet\*) and (marker\* or count\* or ratio\* or level\*)).af.

699594

2

(NLR or PLR).af.

6621

3

exp leukocyte count/

174463

4

1 or 2 or 3

709372

5

exp malignant neoplasm/

2040260

6

(cancer or neoplasm\*).af.

4032374

7

5 or 6

4510877

8

4 and 7

178043

9

exp review/

2296241

10

(literature adj3 review$).ti,ab.

293937

11

exp meta analysis/

127001

12

exp "Systematic Review"/

138332

13

9 or 10 or 11 or 12

2535132

14

(medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.

181082

15

RETRACTED ARTICLE/

8443

16

14 or 15

189422

17

13 and 16

141738

18

(systematic$ adj2 (review$ or overview)).ti,ab.

136877

19

(meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.

145613

20

17 or 18 or 19

283760

21

8 and 20

1510

* Quality assessment of selected studies
  + Assessment was performed by one observer and checked by another.
  + The quality of each study was rated according to ROBIS (http://www.sciencedirect.com/science/article/pii/S089543561500308X)
* Data extraction
  + For each meta-analysis we extracted the first author, year of publication, objectives of review, type of review, participant details, setting and context, number of databases searched, date range of database search, publication date range of studies included, number of studies included, types of studies included, country of origin of studies included, measurement technique in primary studies, outcomes reported that are relevant to umbrella review question, method of data synthesis. This is all detailed in “Table of Included Review Characteristics”.
  + Data required:
    - Primary outcome, total WBC counts associated with cancer sites:
      1. Total WBC count and cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. Pooled (overall effect estimate) relative risk/hazard ratios of cancer mortality and 95% CI
    - Secondary outcome, WBC subsets associated with cancer sites:
      1. Cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. WBC subset categories (lymphocyte count)
      3. Outcomes: pooled hazard ratio and 95% CI for overall survival, disease-free survival, and progression-free survival
    - Tertiary outcome, WBC ratios associated with cancer sites:
      1. Cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. WBC ratio categories (NLR, PLR)
      3. Outcomes: pooled hazard ratio and95% CI for overall survival, disease-free survival, and progression-free survival
  + A data extraction form was designed and pilot tested.
  + Data was requested to corresponding authors by email if not available in the publication in the required format or scale, and/or extracted using an electronic collection spreadsheet by one researcher and tested for accuracy by another.
* Analysis and presentation of results
  + Show a flow diagram for study selection and a table with a summary table of study characteristics (i.e. Figure 1). Make list of excluded studies available to interested readers.
  + “Table of Included Review Characteristics”
  + “Summary of Evidence Table”, (names indicator, identifies included research synthesis, clear indication of results)
    - Tabular presentation overall effect estimates extracted from systematic reviews
      1. Number of studies that inform the outcome, the number of participants, and the heterogeneity of the findings
    - Stoplight Indicator?
    - Clear indication of overlapping original research must be presented
  + Use GRADE principles to evaluate quality of evidence for each indicator of interest
  + Meta-analysis conducted as deemed appropriate.
    - Calculate pooled results with random effects versus fixed effects model.
    - Forest plot.
* Interpretation of results
  + Consider limitations, including publication and related biases
  + Consider strength of evidence
  + Alternative explanations for results
  + Consider applicability
  + Consider implications for future research
  + Consider an analysis of the strength of causality using Bradford Hill criteria
  + Compare to the magnitude of other similar/comparable studies
* Manuscript:
  + Write according to reporting guidelines depending on study type (Ioannidis, 2009).