Research Protocol

Neutrophil counts and cancer prognosis: an umbrella review and meta-analysis

* Study questions
  + What is the overall value of neutrophils (total count, NLR, or presence in tumours) as predictors of cancer outcomes?
  + How strong is the evidence for cell counts and NLR 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 neutrophil counts and NLR with different cancer outcomes;
  + To evaluate systematic reviews and meta-analyses of observational studies that investigated associations of neutrophil counts and NLR with outcomes (overall survival, disease-free survival, and progression-free survival) in different cancer diagnoses;
  + To summarise the outcomes associated with neutrophil counts and NLR; 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 neutrophil counts to cancer outcomes;
  + Secondary outcomes: the association of NLR with cancer outcomes;
  + Tertiary outcomes: the association of tumour infiltrating neutrophils with cancer outcomes;
* Inclusion and exclusion criteria
  + Participants
    - Defined diagnosis of cancer where neutrophils were measured either around the time of diagnosis, before treatment or at the very least before metastasis (T1-4 N0 M0; or stage 1 or 2).
    - Meta-analysis will be conducted when 2 or more meta-analyses are discovered for the same indicator, outcome, and cancer site.
  + Study designs and quality criteria
    - Systematic reviews and meta-analysis assessing neutrophil 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, treatment status, diet, activity level, location).
    - 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 \_\_\_\_\_; meta-analyses of observational studies in the English language and with full text availability were included.
    - The Cochrane Database was searched up until \_\_\_\_\_; meta-analyses of observational studies in the 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 335 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 530 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.
      6. For Cochrane Database, we derived a list of 277 articles for further inspection and a list of xxx were included.
      7. Additionally, reference lists of relevant articles were manually searched for additional citations not included above.
    - Search details were:
      1. MEDLINE (335 articles):

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| --- | --- | --- |
| 1 | (neutrophil\* or NLR).mp. | 157308 |
| 2 | exp Neutrophils/ | 80592 |
| 3 | 1 or 2 | 157308 |
| 4 | (cancer or neoplasm\*).mp. | 2917260 |
| 5 | exp Neoplasms/ | 3019548 |
| 6 | 4 or 5 | 3418713 |
| 7 | 3 and 6 | 18115 |
| 8 | (review or review,tutorial or review, academic).pt. | 2317298 |
| 9 | (medline or medlars or embase or pubmed or cochrane).tw,sh. | 153318 |
| 10 | (scisearch or psychinfo or psycinfo).tw,sh. | 19068 |
| 11 | (psychlit or psyclit).tw,sh. | 941 |
| 12 | cinahl.tw,sh. | 18166 |
| 13 | ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh. | 10483 |
| 14 | (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh. | 25006 |
| 15 | (pooling or pooled or mantel haenszel).tw,sh. | 80696 |
| 16 | (peto or dersimonian or der simonian or fixed effect).tw,sh. | 5573 |
| 17 | (retraction of publication or retracted publication).pt. | 10748 |
| 18 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 247336 |
| 19 | 8 and 18 | 119972 |
| 20 | meta-analysis.pt. | 81851 |
| 21 | exp Meta-Analysis/ | 81851 |
| 22 | (meta-analys$ or meta analys$ or metaanalys$).tw,sh. | 143122 |
| 23 | (systematic$ adj5 review$).tw,sh. | 117721 |
| 24 | (systematic$ adj5 overview$).tw,sh. | 1506 |
| 25 | (quantitativ$ adj5 review$).tw,sh. | 6275 |
| 26 | (quantitativ$ adj5 overview$).tw,sh. | 257 |
| 27 | (quantitativ$ adj5 synthesis$).tw,sh. | 2020 |
| 28 | (methodologic$ adj5 review$).tw,sh. | 4950 |
| 29 | (methodologic$ adj5 overview$).tw,sh. | 343 |
| 30 | (integrative research review$ or research integration).tw. | 121 |
| 31 | 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 | 222360 |
| 32 | 19 or 31 | 270856 |
| 33 | 7 and 32 | 335 |

* + - 1. EMBASE (530 articles):

|  |  |  |
| --- | --- | --- |
| 1 | (neutrophil\* or NLR).mp. | 235868 |
| 2 | exp neutrophil/ or exp neutrophil count/ | 141146 |
| 3 | 1 or 2 | 235868 |
| 4 | (cancer or neoplasm\*).mp. | 3175771 |
| 5 | exp neoplasm/ | 4083103 |
| 6 | 4 or 5 | 4635335 |
| 7 | 3 and 6 | 39346 |
| 8 | exp review/ | 2312994 |
| 9 | (literature adj3 review$).ti,ab. | 297617 |
| 10 | exp meta analysis/ | 129386 |
| 11 | exp "Systematic Review"/ | 141984 |
| 12 | 8 or 9 or 10 or 11 | 2555123 |
| 13 | (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. | 185068 |
| 14 | RETRACTED ARTICLE/ | 8499 |
| 15 | 13 or 14 | 193461 |
| 16 | 12 and 15 | 144963 |
| 17 | (systematic$ adj2 (review$ or overview)).ti,ab. | 140449 |
| 18 | (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab. | 148921 |
| 19 | 16 or 17 or 18 | 290011 |
| 20 | 7 and 19 | 530 |

* + - 1. Cochrane

|  |  |  |
| --- | --- | --- |
| * 1 | neutrophil\* or NLR | 6792 |
| 2 | MeSH descriptor: [Neutrophils] explode all trees | 1317 |
| 3 | #1 or #2 | 6792 |
| 4 | cancer or neoplasm\* | 125576 |
| 5 | MeSH descriptor: [Neoplasms] explode all trees | 61407 |
| 6 | #4 or #5 | 129873 |
| 7 | #3 and #6 | 2029 |

Cochrane Reviews: 248

Other Reviews: 29

Total Reviews: 277

* 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” specifying the aggregated data from meta-analyses. Studies which have included overlapping primary research studies will be identified. Primary research level study data will only be included if an outcome is only informed by one study.
  + Data required:
    - Primary outcome, total neutrophil counts associated with cancer sites:
      1. Total neutrophil count and cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. Pooled (overall effect estimate) and 95% CI for overall survival, disease-free survival, and progression-free survival
    - Secondary outcome, NLR associated with cancer sites:
      1. Cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. Outcomes: pooled hazard ratio and 95% CI for overall survival, disease-free survival, and progression-free survival
    - Tertiary outcome, tumour infiltrating neutrophils associated with cancer sites:
      1. Cancer site (‘lung’, ‘prostate’, ‘breast’, ‘colorectal’, ‘pancreatic’, ‘gastric’)
      2. 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).