Response to Reviewers' Comments

Reviewer #1

Dear authors! I read with interest your manuscript "Is Neutrophil-to-Lymphocyte Ratio accurate as a prognostic factor for the survival in patients with colorectal liver metastases?", which is a systematic review of the literature. Although there are some pervious similar reviews, your work involved some new aspects and brings new to the field. However, the manuscript evidently needs a revision, including language, format and presentation of data. Please, check that the search words are mentioned correctly ("metastasis?" instead of metastas, NLR instead of neutrophil-lymphocyte ratio, etc), as it may significantly impact the search results. The introduction section does not reflect motivation for the research. In other words, it is not clear why it is necessary to perform this systematic review, despite there are some, published recently (doi: 10.1371/journal.pone.0159447. - in 2016, doi: 10.1002/jso.24523 - in 2017, for example. *I am not a co-author of the mentioned studies). What is a knowledge gap? Please, rewrite this section so that potential readers could realize the novelty of the work you performed and understand its merit. Please, define any abbreviations (OS, RE) at first mention. Please, add information about the screening for duplicate publications and data on cancer of other/mixed origins to the inclusion/exclusion criteria. It is not quite clear which factors were taken to the account for multivariate analysis. Whether cancer type/grade/stage; location, quantity, size of the metastases were considered? The title of the manuscript is misleading. Is it possible to answer the title's question based on the results? The accuracy of prediction was not studied actually. Please, revise. Moreover, the conclusions do not correspond with the study aims (in the abstract, as well as in the manuscript's body). The easiness, simplicity and costs of NLR calculation was not really assessed and thus could not be mentioned there. Could you please add the details on the impact of the study results on practice in the discussion? How the outcomes of different treatment options depend on the initial LNR? Is it possible to elaborate some algorithm for the treatment of hepatic metastases of CRC based on the results? The manuscript requires great deal of language and format polishing.

Response: Thank you. We have taken your comments into consideration and we address each one of them below:

1."However, the manuscript evidently needs a revision, including language, format and presentation of data. Please, check that the search words are mentioned correctly ("metastasis?" instead of metastas, NLR instead of neutrophil-lymphocyte ratio, etc), as it may significantly impact the search results."

Response: Language, format and presentation of data were thoroughly reviewed. Regarding the search terms, truncation is a search method in which symbols are used in place of letters or words to help you broaden your search. In PubMed, the asterisk (*) represents any group of characters, including no character. It can be used at the end of the root of your term (minimum of at least four characters).

   By using the term "metastas*" in the first paragraph of the "Data extraction and risk of bias" section of the "Materials and Methods" we aimed to include in one search the words "metastases" and "metastasis".

2. "The introduction section does not reflect motivation for the research. In other words, it is not clear why it is necessary to perform this systematic review, despite there are some, published recently (doi: 10.1371/journal.pone.0159447. - in 2016, doi: 10.1002/jso.24523 - in 2017, for example. *I am not a co-author of the mentioned studies). What is a knowledge gap? Please, rewrite this section so that potential readers could realize the novelty of the work you performed and understand its merit."

Response: The following paragraph was added to the Introduction section, reflecting the motivation for research and giving details about the knowledge gap:

"In this systematic review we investigated the association between NLR and the prognosis of CRLM in patients treated with interventions of any modality including surgery, chemotherapy and ablative techniques.[9,10] High NLR has been associated with poor survival in CRLM patients in Tang's et al. systematic review and metanalysis which included 8 studies and Haram's et al. systematic review which included 8 studies too. Our systematic review includes 19 studies thus making the analysis' results more robust… Our systematic review consists of 12 studies including 2.442 patients treated surgically, 6 studies including 641 patients treated with RFA or RE or solely chemotherapy and 1 study (Kishi et al.) including 200 patients treated surgically and 90 different patients treated with RFA. We studied the different impact of pretreatment NLR as a prognostic factor depending on the medical intervention and we present the analysis' results in two categories. The first category included 2.642 patients that were treated surgically and the second category included 731 patients that were treated with ablative techniques or solely chemotherapy. All the studies that we included demonstrate that CRLM patients with low pretreatment NLR present better survival and disease-free survival in comparison to high pretreatment NLR patients regardless of the medical intervention that they were submitted to."

3."Please, define any abbreviations (OS, RE) at first mention."

Response: Abbreviations are defined at first mention.

4."Please, add information about the screening for duplicate publications and data on cancer of other/mixed origins to the inclusion/exclusion criteria.

Response: In the second paragraph of the "Data extraction and risk of bias" section of the "Materials and Methods" we changed: "The titles of the articles were screened and relevant abstracts were then reviewed. Eligible articles were further evaluated and then the references of those studies were also checked." to: "The titles of the articles were screened and relevant abstracts were assessed for eligibility. After excluding duplicates, eligible articles…"

  Cancer of other/mixed origins is not part of our research, therefore the following was added to the exclusion criteria: "2) patients with liver metastases originating from outside the colorectum"

5.It is not quite clear which factors were taken to the account for multivariate analysis. Whether cancer type/grade/stage; location, quantity, size of the metastases were considered?" πουλο

Response: Our study includes CRLM patients treated surgically or non surgically. We did NOT perform univariate or multivariate analysis. We analyzed results from 18 studies (data are shown in tables 3 and 6) that conducted univariate as well as multivariate analysis. For the multivariate analyses multiple criteria were considered, including but not limited to "sex", "age", "tumor size", "extrahepatic spread of disease", "number of metastases at liver", "surgical margin status", "presurgical NLR", "postsurgical NLR" etc.

6."The title of the manuscript is misleading. Is it possible to answer the title's question based on the results? The accuracy of prediction was not studied actually. Please, revise."

Response: The title of the manuscript was properly adjusted from: "Is Neutrophil-to-Lymphocyte Ratio accurate as a prognostic factor for the survival and tumor recurrence in patients with colorectal liver metastases? to " Neutrophil-to-Lymphocyte ratio as a prognostic factor for the survival in patients with colorectal liver metastases: a systematic review."

7."Moreover, the conclusions do not correspond with the study aims (in the abstract, as well as in the manuscript's body). The easiness, simplicity and costs of NLR calculation was not really assessed and thus could not be mentioned there."

Response: In the "conclusion" section of the Discussion in the manusxript's body we changed:
"... adjusted to benefit the patient. The measurement is simple, easy and inexpensive and can be applied prior to chemotherapy or prior to surgery. Larger studies could help identify a standard, widely accepted cut-off value and therefore make NLR's prognostic significance applicable in clinical practice." to "...adjusted to benefit the patient. Overall, high pretreatment NLR was significantly associated with worse OS and DFS. Larger studies could help…"

   We also added the following paragraph in the "association between NLR - inlammation - cancer" section of the Discussion:

   "NLR is an inexpensive and easily calculated marker by dividing the total count of neutrophils by the total count of lymphocytes in peripheral blood as measured in a complete blood count (CBC) exam. NLR is also immediately available since a CBC exam is part of routine exams in patients with cancer."

   The NLR is an easily calculated and low cost biomarker, as stated in Tang's et al. and Haram's et al. systematic reviews.

   In the "conclusion" section of the Abstract we changed:
"NLR is an easily accessible, low-cost biomarker that demonstrates considerable prognostic value. Elevated pretreatment NLR is associated with poor OS and DFS in all patients with CRLM within different approaches of medical treatment." to "NLR is an inflammatory biomarker that demonstrates considerable prognostic value. Elevated pretreatment NLR is associated with poor OS and DFS in patients with CRLM who are submitted to different treatments."

8."Could you please add the details on the impact of the study results on practice in the discussion?

Response: In the "Discussion" in the "impact on clinical practice" section we added the following two paragraphs:

"NLR is an easily calculated tool with a possible prognostic significance. High NLR could inform the clinicians about the worse OS and DFS that would be expected. Since worse DFS would be expected, patients with high NLR could be submitted to earlier and more frequent diagnostic imaging exams, in order to diagnose disease recurrence. Moreover, better prognosis would be anticipated in patients with low NLR since they present better OS and DFS.

Moreover, some patients are initially diagnosed with unresectable or potentially resectable CRLM. Many studies have shown that inoperable CRLM can be down-staged to resectable CRLM after chemotherapy, but this happens in less than 35% of patients with inoperable CRLM. Therefore, more than 65% of the patients with unresectable CRLM will not benefit from chemotherapy and it would be important to identify biomarkers that would recognize chemosensitive patients. Later on, those patients would be submitted to secondary CRLM curative resection. Wu et al. and Mao et al. demonstrated in their studies that the normalization of NLR after chemotherapy is correlated to chemosensitivity. Consequently, NLR could be used as an assisting tool in stratifying the patients as chemosensitive or chemoresistant. Chemoresistant patients would possibly benefit more from interventions such as RFA or RE rather than chemotherapy. More studies are needed to assess whether NLR can be used as an indicator of chemosensitivity or if NLR could be combined with other biomarkers to increase accuracy."

9. How the outcomes of different treatment options depend on the initial LNR?

Response: The following paragraph was added in the "impact on clinical practice" section of the "Discussion":

"Our results clearly demonstrate that elevated NLR is associated with adverse OS and DFS. These results are significant and they are the same across heterogeneous studies that included different populations, age groups, cancer stages, chemotherapy regimens and medical interventions, which shows that NLR could be an important prognostic factor that could be used in CRLM patients. High pretreatment NLR is associated with worse outcomes independently of the treatment that the patients were submitted to."

10. Is it possible to elaborate some algorithm for the treatment of hepatic metastases of CRC based on the results?"

Response: The following paragraph was added to the discussion section:

   "Prospective studies are needed in order to examine whether NLR could be used as part of an algorithm for the treatment of CRLM. It could also be used in combination with other biomarkers or parameters such as CEA, CA19-9, primary tumor location and primary tumor TNM stage, which have been used in other studies in order to create a novel scoring system that would improve the predictive accuracy of recurrence and survival."

Reviewer #2
Not registered in PROSPERO.

Response: Thank you for your response. We have not registered our systematic review in PROSPERO. This is something we should have done at the time of conception of the idea for the systematic review. Right now we cannot register our systematic review in PROSPERO as it does not fit the inclusion criteria of PROSPERO because it is a completed systematic review. We hope this will not be a problem since registration in PROSPERO is not a requirement for a systematic review's publication in the World Journal of Clinical Oncology.