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Reviewer A

Comment 1: This is a novel study from a Mexican population which adds to the existing evidence base by suggesting that LAR may be a potential prognostic indicator for 3 year survival in patients newly diagnosed with classic Hodgkin Lymphoma. I think this is an important finding and, as the authors themselves recognize, warrants validation in a larger population to verify the findings.

Reply 1: Thank you very much for your comments.

Comment 2: My main statement is that, due to the rarity of Hodgkin Lymphoma, the sample size is very small in this study (44 patients) and I do not think it is powered to make estimations/recommendations from Kaplan Meier/ROC curves. Statements are made regarding LLR and LAR but the confidence intervals are extremely large and in the KM curves are almost completely overlapping at all time points. This is even more of an issue when the authors further stratify by stage.

The estimates presented from the cox proportional hazard models are more reliable and accurate. These provide novel, informative and potentially promising results (albeit with wide confidence intervals).

Reply 2: We agree with the reviewer. The confidence intervals of LLR and LAR are extremely large, and the Kaplan-Meier curve almost completely overlaps at all time points. Our study´s log-rank test for the NLR, PLR, SII, PNI, and NAR was $p>0.05$; thus, the Kaplan-Meier curves are not statistically significantly different. This is likely because such small sample does not have the power to rule out a real difference and avoid a type-two error (1). On the other hand, LLR, LAR (in all patients and stratified patients), PAR had a log-rank test with $p<0.05$. However, the wide confidence intervals limit statistical conclusions. Another method of comparing Kaplan-Meier curves is using the HR, which gives a relative event rate in the groups (1). In this sense, only LAR was an independent prognostic indicator for OS in cHL patients. Nevertheless, it should be noted that given the relatively small number of cHL patients, the multivariable Cox proportional hazard regression model applied in this study may be too conservative or lack enough power to distinguish the prognostic indicators in terms of survival outcomes. More studies in larger patient populations are needed to improve predictions and more accurately estimate effect size, let alone to demonstrate clinical value.
This response was included in this new submission (Discussion section). Moreover, figures 1, 2, and 3 were modified to reflect the prognostic value of the ratios.

Changes in the text: We added some data in the Discussion section (see Page 7, lines 213-225):
"Third, our study´s log-rank test for the NLR, PLR, SII, PNI, and NAR was p>0.05; thus, the

Kaplan-Meier curves are not statistically significantly different. This is likely because such small sample does not have the power to rule out a real difference and avoid a type-two error (19). On the other hand, LLR, LAR (in all patients and stratified patients), PAR had a log-rank test with $p<0.05$. However, the wide confidence intervals limit statistical conclusions. Another method of comparing Kaplan-Meier curves is using the HR, which gives a relative event rate in the groups (19). In this sense, only LAR was an independent prognostic indicator for OS in cHL patients. Nevertheless, it should be noted that given the relatively small number of cHL patients, the multivariable Cox proportional hazard regression model applied in this study may be too conservative or lack enough power to distinguish the prognostic indicators in terms of survival outcomes. More studies in larger patient populations are needed to improve predictions and more accurately estimate effect size, let alone to demonstrate clinical value."

Moreover, we have modified our figures to reflect the prognostic value of the ratios (see Figures 1, 2 and 3).

Comment 3: Minor English corrections occur in the manuscript.

Specific comments are listed below for consideration (page and line numbers refer to the PDF number on the bottom of the page and line numbers down the left side):

Abstract:
Para 1 line 10: "To evaluate the prognostic significance of lactate Dehydrogenase albumin ratio in patients with cHL" consider adding This study aims to at the beginning of this sentence.

Reply 3: In this new submission the sentence "To evaluate the prognostic significance of lactate Dehydrogenase albumin ratio in patients with cHL" was changed to "This study aims to evaluate the prognostic significance of lactate dehydrogenase/albumin ratio in patients with cHL", as suggested by the reviewer.

Changes in the text: We have modified our text as advised (see Page 1, line 9):
"This study aims to evaluate the prognostic significance of LAR in patients with cHL".

Comment 4: Page 1 line 14: the prognostic value of LAR for what ?cHL overall survival. Please specify.

Reply 4: We wanted to say: "… the prognostic value of LAR for cHL overall survival."

Changes in the text: We have modified our text as advised (see Page 1, line 12):

"... the prognostic value of LAR for cHL OS."

Comment 5: Page 1 line 15: please specify the abbreviations when they are first used e.g. LLR and HR.

Reply 5: In this new submission, the abbreviations were specified when they are first used.

Changes in the text: We have modified our text as advised (see Page 1, lines 13-17):

"Univariate Cox regression analysis demonstrated that LLR (serum lactate dehydrogenase level (U/L)/ absolute lymphocyte count [x109/L]) >260.91 (Hazard Ratio (HR)= 5.567, 95% confidence interval (CI): 1.217-25.459, p< 0.05), and LAR (serum lactate dehydrogenase level [U/L]/albumin level [g/L]) >12.5 (HR= 23.693, 95% CI: 3.126-179.578, p< 0.005) were significant prognostic factors for OS."

Comment 6: Page 1 line 15: please specify the units for the blood tests.

Reply 6: The units for the blood test were included in this new submission.

Changes in the text: We have modified our text as advised (see Page 1, lines 13-17):

"Univariate Cox regression analysis demonstrated that LLR (serum lactate dehydrogenase level (U/L)/ absolute lymphocyte count [x10^9/L]) >260.91 (Hazard Ratio (HR)= 5.567, 95% confidence interval (CI): 1.217-25.459, p< 0.05), and LAR (serum lactate dehydrogenase level [U/L]/albumin level [g/L]) >12.5 (HR= 23.693, 95% CI: 3.126-179.578, p< 0.005) were significant prognostic factors for OS."

Comment 7:
Background:

Page 2 line 41: consider replacing "establishing a follow-up" to long term monitoring and surveillance.

Reply 7: In this new submission, the sentence "establishing a follow-up" was replaced to "long term monitoring and surveillance."

Changes in the text: We have modified our text as advised (see Page 2, lines 39-40):

"...sensitive non-invasive diagnostic tests remains a significant obstacle to long term monitoring and surveillance of patients with cHL."

Comment 8: Page 2 line 43: replace 'prognostic' with prognosis

Reply 8: In this new submission, the word "'prognostic" was replaced by "prognosis"

Changes in the text: We have modified our text as advised (see Page 2, line 42):

"...fast prognosis of cHL. cHL progression and prognosis are complex, with many contributing

factors…"

Comment 9:
Methods:

Page 2 line 54: please specify which electronic medical records were used, I presume hospital. Was this a single or multi-centre study.

Reply 9: We specify that the electronic medical records from Hospital and that this was a single-center study.

Changes in the text: We have modified our text as advised (see Page 2, lines 53-58):

"This was a single-center retrospective study performed at a tertiary hospital in Mexico (UMAE Hospital de Especialidades No. 14, Centro Médico Nacional "Adolfo Ruiz Cortines"). Data of 44 patients with newly diagnosed and untreated cHL between January 2015 and January 2022 were evaluated. Overall survival (OS) was defined as the period from diagnosis until the date of last follow-up or death due to any cause. Follow-up data of the patients were obtained using the electronic medical records from hospital, follow-up visits, or by phone call."

Comment 10:
Results:

Page 4 line 109: 1 decimal place for percentages is sufficient. Please check the percentage sign (%) is included for all values as it appears to be missing in some places in the first paragraph.

Reply 10: 1 decimal place for percentage and the percentage sign (%) were included in this new submission.

Changes in the text: We have modified our text as advised (see Page 4, lines 114-118):

"The forty-four patients (26 females and18 males) were classified using the Ann Arbor staining system as early-stage (stage I/II) and advanced-stage (stage III/IV) cHL. Most patients had advanced-stage cHL (26 cases, 59.0%). Both groups' mean age was 34 years old [IQR 27-43] (p= 1). The predominant histology was nodular sclerosis HL in 12 (66.6%) and 17 (65.3%) patients with early-stage and advanced-stage cHL, respectively."

Comment 11:
Page 4 line 112: the authors state "more likely" but present?mean levels. Replace with "on average had…." And then in brackets state if the presented estimates are medians or means.

Reply 11: We make the changes suggested by the reviewer.

Changes in the text: We have modified our text as advised (see Page 4, lines 118-122):

"Regarding pretreatment blood test findings, patients with advanced-stage cHL, on average, had to have decreased neutrophils (means= 7.61 x109/L vs 7.30 x109/L, p<0.0001), albumin (means= 41.11 g/L vs 34.92 g/L, p= 0.002) and PNI (means= 49.39 vs 41.76, p= 0.001), and an increased LDH (medians= 165 U/L vs 255 U/L, p= 0.03), and LAR (medians= 4.14 vs 7.25, p<0.0005)."

Comment 12:
Page 4 line 148: what does not reached mean here? How can survival be compared if estimates were not produced?

Reply 12: The word "not reached" was removed in this new submission. The survival estimates were calculated using the log rank test.

Changes in the text: We have modified our text as advised (see Page 5, lines 148-149):

"The survival estimates were calculated using the log rank test."

Comment 13:
Page 5 line 143: I believe the authors mean the 3 year survival was lower not shorter, but then they present the estimate of 88.4% vs 0%. I presume this is presented the wrong way around and should read (0 to 88.4%)? Does this mean that no patients with high LAR and stage III/IV disease survived 3 years? If so state this. I feel more details can be provided on actual survival times from the Kaplan meier.

Reply 13: This observation is correct. The 3-year OS was significantly shorter in patients with high LAR (>12.5) compared with patients with low LAR in stages III/IV (0% vs. 88.4%; p< 0.005). This sentence was corrected in this new submission. Moreover, the patients with high LAR and stage III/IV disease did not survive after 3 years of follow-up.

Changes in the text: We have modified our text as advised (see Page 5, lines 153-156):

"The 3-year OS was significantly shorter in patients with high LAR (>12.5) compared with patients with low LAR in stages III/IV (0% vs. 88.4%; p< 0.005) (Figure 3B). The patients with high LAR and stage III/IV disease did not survive after 3 years of follow-up."

Comment 14:
Discussion:

Page 6 line 200: The authors acknowledge the small sample size of the study. I feel as this is a key limitation the implications of this on the findings need to be expanded on.

Reply 14: The implications of the small sample are discussed in greater detail about the implications for the findings.

Changes in the text: We have modified our text as advised (see Page 7, lines 213-225):

"Third, our study's log-rank test for the NLR, PLR, SII, PNI, and NAR was p>0.05; thus, the Kaplan-Meier curves are not statistically significantly different. This is likely because such small sample does not have the power to rule out a real difference and avoid a type-two error (19). On the other hand, LLR, LAR (in all patients and stratified patients), PAR had a log-rank test with p<0.05. However, the wide confidence intervals limit statistical conclusions. Another method of comparing Kaplan-Meier curves is using the HR, which gives a relative event rate in the groups (19). In this sense, only LAR was an independent prognostic indicator for OS in cHL patients. Nevertheless, it should be noted that given the relatively small number of cHL patients, the multivariable Cox proportional hazard regression model applied in this study may be too conservative or lack enough power to distinguish the prognostic indicators in terms of survival outcomes. More studies in larger patient populations are needed to improve predictions and more accurately estimate effect size, let alone to demonstrate clinical value."

Reviewer B

Comment 1:
Thank you for allowing me to re-read your article:
Overall it's easy to read and clearly presented.

Reply 1: Thank you very much for your comments.

Here are a few comments:

Comment 2:
- in the abstract: could you replace LLR with "serum lactate dehydrogenase level"?

Reply 2: We replaced LLR with "serum lactate dehydrogenase level" in this new submission, as suggested by the reviewer.

Changes in the text: We have modified our text as advised (see Page 1, lines 13-14):

"... LLR (serum lactate dehydrogenase level (U/L)/ absolute lymphocyte count [x109/L]..."

Comment 3:
- the prognostic value of LAR should be reviewed in solid tumours and other lymphomas in the introduction part rather than in the discussion.

Reply 3: We agree with the reviewer. Thus, the prognostic value of LAR was reviewed in solid tumours and other lymphomas in the introduction.

Changes in the text: We have modified our text as advised (see Page 2, lines 43-49):

"Recently, lactate dehydrogenase-to-albumin ratio (LAR) has been demonstrated to be prognostic of overall survival (OS) in patients with colon cancer, esophageal cancer, colorectal carcinoma, and pancreatic cancer, with optimal cut-off values of 4.91, 5.5, 5.27, and 6.5, respectively (3–6). A 5-years OS of 13.3% was related to patients with LAR >5.5 (5). On the other hand, a 2.5-years OS of 55.2% in the group with high LAR (>5.27) was determined (4). The 3-years and 5-years OS were 56% and 44% in the high LAR group (>4.91), respectively, was reported by Xi et al (3)."

Comment 3:
- Concerning the chemotherapy protocols used, please give the names of the molecules in the appendix and specify whether the use of Rituximab is reserved for a subclass of lymphoma (CD20 expression?).

Reply 3: The names of the molecules were included in this new submission. Second, the rituximab combined with chemotherapy was the first-line induction therapy of CD20 positive cHL.

Changes in the text: We have modified our text as advised (see Pages 2-3, lines 65-78):

"... patients with samples analyzed using a panel of antibodies specific for CD15 (lewis X antigen) and CD30 (Ki-1 antigen), which are necessary to provide a confident diagnosis. In addition, the patients were eligible for the study if they had performed a positron emission tomography/computed tomography (PET/CT) according to local protocols and scanner procedures. Patients were stratified into early-stage (I-II) and advanced-stage (III-IV) cHL according to the Ann Arbor staging system.

The patients with early-stage cHL were treated with six cycles of ABVD (Doxorubicin [Adriamycin], Bleomycin, Vinblastine, and Dacarbazine) and rituximab-ABVD. Patients with advanced-stage cHL were treated with six to eight cycles of BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone), LOPP-ABV (Lomustine, Vincristine, Procarbazine, Prednisone), rituximab-BEACOPP or escalated BEACOPP (eBEACOPP) regimens. Rituximab combined with chemotherapy was the first-line induction therapy of CD20 positive cHL."

Comment 4:
- the sedimentation rate is a classic prognostic marker in Hodgkin's lymphoma: why was it not compared with the LAR in the population?

Reply 4: In this study, the hazard ratio for erythrocyte sedimentation rate (ESR) was calculated; however, this value was not statistically significant (HR= 2.61, 95% IC: 0.56-12.07; P= 0.219). Thus, the ESR had no prognostic importance in this population.

Changes in the text: We have modified our text as advised (see Page 4, lines 130-132):

"Although, the erythrocyte sedimentation rate (ESR) is a prognostic factor in Hodgkin´s lymphoma, this had no prognostic importance in this population (HR= 2.61, 95% IC: 0.56-12.07, p= 0.219)."

Comment 5:
- Is there an impact of different treatments on patient prognosis: can the negative prognostic value of LAR be erased by a more aggressive treatment?

Reply 5: We agree with the reviewer, the impact of different treatments on patient could modulate the prognostic value of LAR. Thus, studies of patients with various types of treatment or more aggressive treatments are needed to evaluate the predictive capability of LAR in the prognosis of cHL.

Changes in the text: We have modified our text as advised (see Page 7, lines 225-228):

"Furthermore, the impact of different treatments on patient could modulate the prognostic value of LAR. Thus, studies of patients with various types of treatment or more aggressive treatments are needed to evaluate the predictive capability of LAR in the prognosis of cHL."

Comment 6:
- Is a prospective study planned for the future?

Reply 6: More studies in larger patient populations are needed to improve predictions and more accurately estimate effect size, let alone to demonstrate clinical value.

Changes in the text: We have modified our text as advised (see Page 7, lines 223-225):

"More studies in larger patient populations are needed to improve predictions and more accurately estimate effect size, let alone to demonstrate clinical value."

Comment 7:
- What are the next steps if the prognostic value of LAR is confirmed?

Reply 7: If the prognostic value of LAR is confirmed, a multi-center prospective study to characterize and validate the LAR for predicting worsening in patients with cHL is the next step.

Changes in the text: We have modified our text as advised (see Page 7, lines 235-237):

"If the prognostic value of LAR is confirmed, a multi-center prospective study to characterize and validate the LAR for predicting worsening in patients with cHL is the next step."

References

1. Rich Jt, Neely Jg, Paniello Rc, et al. A Practical Guide To Understanding Kaplan-Meier Curves. Otolaryngol Head Neck Surg. septiembre de 2010;143(3):331-6.