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| **QUIPS Risk of Bias Assessment Instrument for Prognostic Factor Studies** | | |  |  |
| *Modified from:* Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437, with the assistance of the QUIPS-LBP Working Group. | | |  |  |
| **Author and year of publication** | Aloisio 2020 |  |  |  |
| **Study identifier** |  |  |  |  |
| **Reviewer** |  |  |  |  |
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| **Biases** | **Issues to consider for judging overall rating of "Risk of bias"** | **Study Methods & Comments** | **Rating of reporting** | **Rating of "Risk of bias"** |
| Instructions to assess the risk of each potential bias: | These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains. | Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow. |  |  |
| **1. Study Participation** | **Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).** |  |  |  |
| *Source of target population* | The source population or population of interest is adequately described for key characteristics (LIST). | “Adult (age<18 years) COVID-19 patients admitted between February 21 and March 31, 2020, to the ‘‘Luigi Sacco’’ academic hospital in Milan, 1 of the 2 national reference centers for infectious diseases in Italy. Patients were hospitalized in 1 of the following isolation wards reserved exclusively for COVID-19 care: 1 ICU, 2 infectious disease units, 1 pulmonology unit, and 4 low-medium intensity care wards. All patients had clinical and/or radiologic findings highly suggestive for COVID-19 at admission, and SARS-CoV-2 infection was confirmed by detection of viral RNA on nasopharyngeal material, using a real-time reverse transcription polymerase chain reaction method.” | Yes |  |
| *Method used to identify population* | The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care) | Retrospective, observational study.  “Patients’ data were extracted from the hospital information systems.” | Yes |  |
| *Recruitment period* | Period of recruitment is adequately described | February 21 and March 31, 2020 | Yes |  |
| *Place of recruitment* | Place of recruitment (setting and geographic location) are adequately described | ‘‘Luigi Sacco’’ academic hospital in Milan, Italy.  “Patients were hospitalized in 1 of the following isolation wards reserved exclusively for COVID-19 care: 1 ICU, 2 infectious disease units, 1 pulmonology unit, and 4 low-medium intensity care wards.” | Yes |  |
| *Inclusion and exclusion criteria* | Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or “zero time” description). | Adult (age<18 years) COVID-19 patients admitted to hospital.  All patients had clinical and/or radiologic findings highly suggestive for COVID-19 at admission, and SARS-CoV-2 infection was confirmed by detection of viral RNA on nasopharyngeal material, using a real-time reverse transcription polymerase chain reaction method.  Patients still hospitalized at start of data-collection were excluded. | Yes |  |
| *Adequate study participation* | There is adequate participation in the study by eligible individuals | This is a retrospective study. It is unclear whether every patient admitted to the hospital was considered for inclusion in the study. | Unsure |  |
| *Baseline characteristics* | The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics (LIST). | Baseline descriptives described in Table 1. Information about COVID-19 severity is very limited. | Partial |  |
| **Summary Study participation** | **The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.** | Study population accurately described. |  | Low |
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| **2. Study Attrition** | **Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).** |  |  |  |
| *Proportion of baseline sample available for analysis* | Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. | 91 out of 581 patients were excluded because they were still hospitalized at start of data-collection. | No |  |
| *Attempts to collect information on participants who dropped out* | Attempts to collect information on participants who dropped out of the study are described. |  | No |  |
| *Reasons and potential impact of subjects lost to follow-up* | Reasons for loss to follow-up are provided. | They were still hospitalized. | Yes |  |
| *Outcome and prognostic factor information on those lost to follow-up* | Participants lost to follow-up are adequately described for key characteristics (LIST). | They are not described. | No |  |
| There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not. | Not described. | Unsure |  |
| **Study Attrition Summary** | **Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.** | 91 out of 581 patients were excluded because they were still hospitalized at start of data-collection. It could be that these are more severely ill patients and therefore had to stay in the hospital.  You could argue whether you would score this in domain 1 (study participation) or domain 2 (study attrition). If this would have been a prospective study, it was clear that this is a problem of study attrition. Now that it is a retrospective study, it is not so clear anymore. |  | High |
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| **3. Prognostic Factor Measurement** | **Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).** |  |  |  |
| *Definition of the PF* | A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). | “Albumin, CRP, and LDH were measured on the Alinity platform (Abbott Diagnostics) by using immunoturbidimetry (CRP and albumin) and enzymatic (LDH) assays, respectively.”  “Because more than 1 test result was available for each patient, the worst result of the whole hospitalization period was considered for analysis (ie, the highest result for all evaluated analytes except for albumin, for which the lowest result was selected).” | Yes |  |
| *Valid and Reliable Measurement of PF* | Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). | Standard diagnostic platforms and assays were used. They refer to data about analytic performance. | Yes |  |
| Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used. | Optimum biomarker cutoffs both for predicting death and for excluding necessity for intensive care were extrapolated from a receiver operating characteristic (ROC) analysis, by maximizing specificity (outcome 1) and sensitivity (outcome 2), respectively. | no |  |
| *Method and Setting of PF Measurement* | The method and setting of measurement of PF is the same for all study participants. | This is not explicitly described, however, this is a single center study and therefore we can assume this was similar for all participants | Yes |  |
| *Proportion of data on PF available for analysis* | Adequate proportion of the study sample has complete data for PF variable. | See Table 2. For albumin, data are available for 390 out of 427 participants. | No |  |
| *Method used for missing data* | Appropriate methods of imputation are used for missing 'PF' data. | It is not described how missing data were handled. | Unsure |  |
| **PF Measurement Summary** | ***PF* is adequately measured in study participants to sufficiently limit potential bias.** | In case more than 1 test result was available, the worst result was taken. This is not representative for the situation in which the PF will be used. |  | High |
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| **4. Outcome Measurement** | **Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).** | Outcome: mortality |  |  |
| *Definition of the Outcome* | A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct. | In-hospital mortality. | Yes |  |
| *Valid and Reliable Measurement of Outcome* | The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). | Not clearly stated, but it is a very objective outcome. | Yes |  |
| *Method and Setting of Outcome Measurement* | The method and setting of outcome measurement is the same for all study participants. | Not explicitly stated, but we can assume this is stated in patient records. | Partial |  |
| **Outcome Measurement Summary** | ***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.** | Information about outcome assessment is very limited, however, this is a very objective outcome that will very likely be appropriately recorded in patient records, so therefore, low risk of bias. |  | Low |
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| **5. Covariate adjustment** | **Goal: To judge the risk of bias due to inappropriate covariate adjustment (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).** |  |  |  |
| *Important covariates Measured* | All important covariates, including treatments (key variables in conceptual model: LIST), are measured. | Covariates considered are age, CRP, LDH, d-dimer, albumin, ferritin, troponin-T. Other important covariates, such as gender, smoking and comorbidities were not included. | No |  |
| *Definition of the covariate* | Clear definitions of the important covariates measured are provided (e.g., including dose, level, and duration of exposures). | Measurement methods for blood biomarkers were reported. They also give cut-off levels in the methods section for the biomarkers. | Yes |  |
| *Valid and Reliable Measurement of covariates* | Measurement of all important covariates is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). | Standardized diagnostic platforms and assays were used. | Yes |  |
| *Method and Setting of Covariate Measurement* | The method and setting of covariate measurement are the same for all study participants. | This is not explicitly described, however, this is a single center study and therefore we can assume this was similar for all participants. | Unsure |  |
| *Method used for missing data* | Appropriate methods are used if imputation is used for missing covariate data. | Only 72 patients out of 427 (!) had complete data to build a multivariate model. | No |  |
| *Appropriate Accounting for Covariates* | Important covariates are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). | This is not described, so we assume here that it is not done. | No |  |
| Important covariates are accounted for in the analysis (i.e., appropriate adjustment). | “Univariate logistic regression was used to estimate variables’ odds ratios (ORs) and their 95% confidence intervals (CIs) in relation to the selected outcome. A multivariate logistic regression model was then applied to variables significant at the univariate analysis. Final selection of variables included in the multivariate model was done by applying a stepwise approach. A P value <.05 denoted statistical significance.” | Partial |  |
| **Covariate adjustment Summary** | **Important covariates are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.** | The analyses were not accounted for other important covariates such as gender and comorbidities. The majority of participants had to be excluded from multivariable analyses because of missing data. |  | High |
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| **6. Statistical Analysis and Reporting** | **Goal: To judge the risk of bias related to the statistical analysis and presentation of results.** |  |  |  |
| *Presentation of analytical strategy* | There is sufficient presentation of data to assess the adequacy of the analysis. | See Tables and Figures. | Yes |  |
| *Model development strategy* | The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model. | “Univariate logistic regression was used to estimate variables’ odds ratios (ORs) and their 95% confidence intervals (CIs) in relation to the selected outcome. A multivariate logistic regression model was then applied to variables significant at the univariate analysis. Final selection of variables included in the multivariate model was done by applying a stepwise approach. A P value <.05 denoted statistical significance.”  There is univariable pre-selection of predictors which might result in missing important covariates. | No |  |
| The selected statistical model is adequate for the design of the study. | Multivariable logistic regression was used. That is adequate for short-term outcomes.  Note that the authors (wrongly) call this multivariate logistic regression instead of multivariable. | Yes |  |
| *Reporting of results* | There is no selective reporting of results. | There is no study protocol, but all analyses described in methods have been presented in results. | Unsure |  |
| **Statistical Analysis and Presentation Summary** | **The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.** |  |  | High |
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| Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437. | | |  |  |