**Appendix 1 - Quality in Prognostic Studies (QUIPS) Tool**

|  |  |  |
| --- | --- | --- |
| **Domains** | **Prompting items for Consideration** | **Ratings** |
| **Study Participation** | * Adequate participation in the study by eligible persons * Description of the source population or population of interest * Description of the baseline study sample * Adequate description of the sampling frame and recruitment * Adequate description of the period and place of recruitment * Adequate description of inclusion and exclusion criteria | **High bias:** The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants  **Moderate bias**: The relationship between the  PF and outcome may be different for participants and eligible nonparticipants  **Low bias**: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants |
| **Study Attrition** | * Adequate response rate for study participants * Description of attempts to collect information on participants who dropped out * Reasons for loss to follow-up are provided * Adequate description of participants lost to follow-up * There are no important differences between participants who completed the study and those who did not | **High bias**: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants  **Moderate bias**: The relationship between the PF and outcome may be different for completing and non-completing participants  **Low bias**: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants |
| **Prognostic Factor Measurement** | * A clear definition or description of the PF is provided * Method of PF measurement is adequately valid and reliable * Continuous variables are reported or appropriate cut points are used * The method and setting of measurement of PF is the same for all study participants * Adequate proportion of the study sample has complete data for the PF * Appropriate methods of imputation are used | **High bias**: The measurement of the PF is very likely to be different for different levels of the outcome of interest  **Moderate bias**: The measurement of  the PF may be different for different levels of the outcome of interest  **Low bias**: The measurement of the PF is unlikely to be different for different levels of the outcome of interest |

**Appendix 2 – PRISMA Guidelines**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. |  |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |  |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. |  |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). |  |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. |  |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow‐up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. |  |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |  |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |  |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta‐analysis). |  |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |  |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |  |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). |  |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency  ) |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section/topic** | | **#** | **Checklist item** | **Reported on page #** |
| Risk of bias across studies | | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |  |
| Additional analyses | | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre‐specified. |  |
| **RESULTS** | | | |  |
| Study selection | | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |  |
| Study characteristics | | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |  |
| Risk of bias within studies | | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |  |
| Results of individual studies | | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |  |
| Synthesis of results | | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |  |
| Risk of bias across studies | | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |  |
| Additional analysis | | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |  |
| **DISCUSSION** | | | |  |
| Summary of evidence | | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |  |
| Limitations | | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |  |
| Conclusions | | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |  |
|  | **FUNDING** | | |  |
| Funding | | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |  |

**Appendix 3 – Search Strategy**

**EMBASE**

'sport injury'/exp OR 'sport'/exp AND ('biological marker'/exp OR 'protein s100b'/exp OR 'neuron specific enolase'/exp OR 'myelin basic protein'/exp OR 'glial fibrillary acidic protein'/exp OR 'creatine kinase bb'/exp OR 'tau protein'/exp)

**PubMED**

("Athletic Injuries"[Mesh] OR "Sports"[Mesh] OR "Sports/injuries"[Mesh] OR sport\*[tiab] OR sport injur\*[tiab] OR Athletic Injur\*[tiab] OR rugby[tiab] OR box\*[tiab] OR wrestl\*[tiab] OR football[tiab] OR ice hockey[tiab]) AND ("S100B protein, human" [Supplementary Concept] OR "S100 Calcium Binding Protein beta Subunit"[Mesh] OR "Phosphopyruvate Hydratase"[Mesh] OR "Myelin Basic Protein"[Mesh] OR "Glial Fibrillary Acidic Protein"[Mesh] OR "Receptors, AMPA"[Mesh] OR "tau Proteins"[Mesh] OR "Creatine Kinase, BB Form"[Mesh] OR "Amyloid beta-Peptides"[Mesh] OR "Tumor Necrosis Factor-alpha"[Mesh] OR S100B protein[tiab] OR S100 Calcium Binding Protein [tiab] OR Phosphopyruvate Hydratase[tiab] OR neuron specific enolase[tiab] OR Myelin Basic Protein[tiab] OR Glial Fibrillary Acidic Protein[tiab] OR Creatine Kinase BB[tiab] OR AMPA Receptor\*[tiab] OR tau Protein\*[tiab] OR Amyloid beta-Peptide\*[tiab] OR Amyloid beta-Protein\*[tiab] OR Tumor Necrosis Factor[tiab])

(wrestl\*[tiab] OR ice hockey[tiab] OR Football[tiab] OR soccer[tiab] OR box\*[tiab] OR rugby[tiab]) AND concussion[tiab]

("Brain Concussion/blood"[Mesh] OR "Brain Injuries/blood"[Mesh]) AND ("Athletic Injuries"[Mesh] OR "Sports"[Mesh] OR "Sports/injuries"[Mesh] OR sport\*[tiab] OR sport injur\*[tiab] OR Athletic Injur\*[tiab] OR rugby[tiab] OR box\*[tiab] OR wrestl\*[tiab] OR football\*[tiab] OR hockey[tiab])

**CINAHL**

(MH "Rugby") OR (MH "Rugby Injuries") OR (MH "Football Injuries") OR (MH "Athletic Injuries") OR (MH "Hockey Injuries") OR (MH "Martial Arts Injuries") OR (MH "Boxing") OR (MH "Boxing Injuries") OR (MH "Wrestling") OR (MH "Soccer") OR (MH "Brain Concussion") OR (MH "Brain Injuries") OR (MH "Right Hemisphere Injuries") OR (MH "Left Hemisphere Injuries") OR (MH "Intracranial Hemorrhage") OR AB ( (sport\* OR sport injur\* OR Athletic Injur\* OR rugby OR box\* OR wrestl\* OR football\* OR ice hockey) ) OR TI ( (sport\* OR sport injur\* OR Athletic Injur\* OR rugby OR box\* OR wrestl\* OR football\* OR ice hockey) )

(MH "Tumor Necrosis Factor") OR (MH "Creatine Kinase") OR TI ( S100B protein OR S100 Calcium Binding Protein OR Phosphopyruvate Hydratase OR neuron specific enolase OR Myelin Basic Protein OR Glial Fibrillary Acidic Protein OR Creatine Kinase BB OR AMPA Receptor\* OR tau Protein\* OR Amyloid beta-Peptide\* OR Amyloid beta-Protein\* OR Tumor Necrosis Factor ) OR AB ( S100B protein OR S100 Calcium Binding Protein OR Phosphopyruvate Hydratase OR neuron specific enolase OR Myelin Basic Protein OR Glial Fibrillary Acidic Protein OR Creatine Kinase BB OR AMPA Receptor\* OR tau Protein\* OR Amyloid beta-Peptide\* OR Amyloid beta-Protein\* OR Tumor Necrosis Factor )