Psychosocial risk factors for increased emergency hospital utilization by sickle cell disease patients: a systematic review protocol

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Jean-Simon Rech[1,2,3] · Prunelle Getten[4] · Nathalie Dzierzynski[5] · François Lionnet[1,3] · Pierre-Yves Boëlle[3,6,7] · Brigitte Ranque[4,8] · Olivier Steichen[1,2,3]

[1]Assistance Publique - Hôpitaux de Paris, Hôpital Tenon, Service de médecine interne, Paris, France, [2]INSERM UMRS 1142, LIMICS, Sorbonne Université, Paris, France, [3]GRC 25 DREPS, Sorbonne Université, Paris, France, [4]INSERM UMRS 970, Université Paris Descartes, Paris, France, [5]Assistance Publique - Hôpitaux de Paris, Hôpital Tenon, Service de psychiatrie, Paris, France, [6]INSERM UMRS 1136, IPLESP, Sorbonne Université, Paris, France, [7]Assistance Publique - Hôpitaux de Paris, Hôpital Saint-Antoine, Service de santé publique, Paris, France, and [8]Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de médecine interne, Paris, France

ABSTRACT

Objective: To assess psychosocial risk factors for increased emergency hospital utilization by sickle cell patients.

Introduction: Emergency hospital utilization by sickle cell disease patients is high but heterogeneous between patients and in a given patient over time. Psychosocial factors affect emergency hospital utilization and are a possible target to improve the management of sickle cell disease.

Inclusion criteria: This review will include all original quantitative studies evaluating the impact of psychosocial risk factors on emergency hospital utilization by sickle cell disease patients. There will be no language restriction.

Methods: PubMed, Embase, CINAHL, PubPsych, LiSSa, and Web of Science will be searched using a peer-reviewed search strategy. Study selection and extraction of data will be performed independently by two authors. Discrepancies will be solved by consensus or, if needed, by a third author. The authors will assess study quality, as well as perform a narrative synthesis of included studies, and where possible, meta-analyses with evaluation of heterogeneity and publication bias.

Systematic review registration number: PROSPERO CRD42019140435

Keywords: anemia; mental disorders; patient admission; risk factors; sickle cell

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Introduction

Sickle cell disease (SCD) is a severe illness that affects an increasing number of newborns worldwide, estimated around 300,000 in 2010 and expected to reach around 400,000 in 2050.[1] Sickle cell disease alters the beta-chain of hemoglobin leading to structural and functional impairment of red cells resulting in acute and chronic complications.[2] The most frequent acute complication is an acute painful episode (APE), also called vaso-occlusive crisis.[3] Other acute complications, such as acute chest syndrome, stroke, bone marrow necrosis, and infections, can be life threatening. Chronic complications arise from the functional impairment of target organs, such as the heart, kidney, retina, and central nervous system.[2]

Acute painful episodes are most often treated at home with appropriate hydration and oral analgesics, but about one third require a visit to the emergency department (ED) for thorough assessment and intravenous pain management.[4] As a result, SCD patients represent a disproportionate number of ED utilizers.[5]

Frequent ED visits and subsequent hospitalizations have dramatic consequences at the patient and community levels. First, high utilization of hospital care is associated with an increased mortality, most

Correspondence: Jean-Simon Rech, jeansimon.rech@aphp.fr

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likely reflecting the severity of the disease and its poor control.[6] The number of days spent in hospital was strongly associated with the risk of mortality in an American prospective cohort over a two-year period: 2.2% mortality in patients hospitalized < 50 days per year; 26.7% mortality in patients hospitalized 50 to 100 days per year; and 54.5% mortality in patients hospitalized > 100 days per year.[7] Second, high utilization negatively impacts the quality of life of SCD patients and results in a loss in educational and professional opportunities.[8,9] Third, frequent emergency visits and opioid demands lead to misconceptions and negative attitudes of caregivers toward SCD patients.[10] These negative attitudes affect the quality of care, and notably the use of appropriate pain medication during APE.[10] Disease-related discrimination is more often perceived by SCD patients who frequently use emergency hospital services.[11] Finally, high utilization induces high health-related costs.[12] Compared to other chronic diseases, the increasing financial burden of SCD is driven by the number of hospital visits rather than the cost of each visit.[3,13] A better knowledge of the determining factors could help reduce hospital utilization and its negative impacts.

Hospital utilization differs between patients and in a given patient over time.[14] Most hospital visits are attributed to a small proportion of SCD patients.[15] A study in New York state in the US identified that 32% of the 18,541 studied patients had only one hospital visit over a nine-year period, while only 16% of patients accounted for more than 10 visits over the same nine-year period.[16] This heterogeneity in emergency hospital utilization is imperfectly predicted by demographic factors, such as sex and age, or factors related to SCD severity, such as genotype, hemoglobin level, previous acute complications, and chronic complications.[14] Moreover, most of these factors are non-modifiable and thus not eligible for preventive or curative interventions.

Factors related to the individual psychological state and to the social environment can be combined into the broader concept of ''psychosocial factors''[17] that may have a positive or a negative impact on health. Psychological factors include mental and behavioral processes, such as coping styles or personality, and mental and behavioral disorders, such as anxiety, mood, or substance abuse disorders. Social factors are related to social position, such as work, education, socioeconomic level or living area, and factors related to interactions with the social environment, such as family support, social isolation, and communalism. Mental disorders and social vulnerability are frequent in SCD patients.[18,19] Previous studies show conflicting results concerning the association between psychosocial risk factors and hospital utilization.[14,20,21] Synthesizing the evidence from multiple available studies evaluating psychosocial risk factors for an increased emergent hospital utilization will help identify high risk situations that can benefit from preventive actions or dedicated management.

A search of PROSPERO, PubMed, and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted and two systematic reviews on closely related topics were identified. The first systematic review shows a significant association between depression and high hospital utilization in children and adults with SCD[22]; however, this review does not consider other mental disorders or sociological risk factors.

The second systematic review addresses all risk factors for high emergency hospital utilization.[18] It does not confirm any association between psychiatric comorbidities and high emergency hospital utilization; however, several pitfalls limit its findings. First, the search strategy did not include free-text terms, resulting in the potential omission of relevant studies[23]; for example, the search did not find several studies included in the previous systematic review on depression. Second, the impact of psychiatric comorbidities on health care utilization was not calculated as such, but only relative to the impact of medical comorbidities, which limits the interpretation and applicability of the results. Third, the systematic review only considered adult SCD patients.

The goal of this review is to perform a systematic review focused on the association between psychosocial risk factors and emergency hospital utilization in both children and adult SCD patients.

Review question

Do psychosocial risk factors increase emergency hospital utilization of SCD adults and children and, if so, to what extent?

Inclusion criteria

Participants

This review will consider studies that include SCD patients of all hemoglobin genotype and all ages.

Studies that include patients with sickle cell trait will be excluded.

Exposures of interest

This review will consider studies that evaluate exposures related to psychosocial factors, including mental and behavioral processes (such as coping or attachment style, personality, etc.); mental and behavioral disorders (such as mood disorders, anxiety disorders, psychotic disorders, stress-related disorders, substance abuse–related disorders, etc.); and social factors (such as education, professional occupation, financial resources, health care insurance, family status, social isolation, living conditions, and social group membership).

The authors expect a high variability in the instruments and methods used to define a psychosocial risk factor across studies. The review will include all studies defining a psychosocial factor with a reproducible method: a scale, questionnaire, set of diagnostic criteria, diagnostic code, or another clearly specified instrument. The definition used by the authors will be assessed during the quality appraisal and specified in the description of included studies.

Outcomes

This review will consider studies that include the level of emergency hospital utilization, defined by the frequency or cumulative duration of emergency visits and hospitalization over a period of time, the time between consecutive emergency visits or hospitalization, or any other relevant indicator. If a study only analyses global hospital utilization (ie, combined emergency and planned hospital utilization), it will be considered for inclusion only if emergency hospital utilization is $\geq$ 80% of all hospital utilization.

Additional outcomes include the types of hospital utilization: ED visits, emergency hospitalization in a medical ward, or emergency hospitalization in an intensive care unit.

Types of studies

This review will include all types of original quantitative observational studies, without language restriction, from database inception. All types of prospective and retrospective observational studies will be considered (cohort, case-control, cross-sectional studies, mixed studies). For the studies published in a language not spoken by the authors, a native speaker of the language will be engaged whenever possible. Authors of relevant studies will be contacted, where required.

Methods

This systematic review will be conducted in accordance with JBI methodology for systematic reviews of etiology and risk.[24] The protocol is registered in PROSPERO (CRD42019140435).

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of PubMed was performed to identify articles on the topic. Text words from the titles and abstracts of relevant articles, and MeSH terms used to index the articles, were used to build a full search strategy for PubMed, which was reviewed using the Peer Review of Electronic Search Strategies: 2015 Guideline Statement[23] (see Appendix I). The search strategy, including all identified text words and indexing terms, will be adapted for each bibliographic database. The reference list of all included studies will be screened for additional relevant references. The searches will be re-run prior to final analyses to look for studies published since the initial searches.

MEDLINE and PMC will be searched through PubMed, Embase through the Elsevier platform and CINAHL, PubPsych, LiSSa, and Web of Science will be searched via their websites. Open Grey database and ProQuest Dissertation and Theses will be searched via their websites for unpublished studies and gray literature.

Study selection

Following the search, all identified citations will be collated and uploaded into JabRef version 4.3.1 (www.jabref.org) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers (JSR, PG) to discard irrelevant references. The full text of the remaining references will be assessed against the inclusion criteria by two independent reviewers (JSR, PG). Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer (OS). The results of the search and selection process, including reasons for exclusion of full text articles, will be reported in a

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[25]

Assessment of methodological quality

The risk of bias of included studies will be appraised by two independent reviewers (JSR, PG) at the study level using the validated Quality In Prognosis Studies (QUIPS) tool.[26] The QUIPS tool for critical appraisal of studies on etiology and risk was chosen for the following reasons: i) QUIPS uses the same instrument for different study designs, and is therefore well suited for a review with multiple study designs; ii) QUIPS provides a detailed checklist for each domain; iii) QUIPS is a widely used tool and is recommended by the Cochrane Prognosis Methods Group, the National Institute for Health and Care Excellence, and the Australian National Health and Medical Research Council.

The QUIPS tool will assess the following domains:

- participation: source of target population, method used to identify the population, recruitment period, place of recruitment, inclusion and exclusion criteria, adequate study participation, baseline characteristics;
- attrition: proportion of baseline sample available for analysis, attempts to collect information on participants who ceased involvement prematurely, reasons and potential impact of subjects lost to follow-up, outcome and prognostic factor information on those lost to follow-up;
- prognostic factor measurement: definition, valid and reliable measurement, settings of measurement, continuous variable handling, proportion of data available for analysis, method used for missing data;
- outcome measurement: definition, valid and reliable measurement, settings of measurement;
- confounding: important confounders measured, definition of the confounding factors, valid and reliable measurement of confounders, method and setting of confounding measurement, method used for missing data, appropriate accounting for confounding in study design and analysis;
- statistical analysis and reporting: presentation of analytical strategy, model development strategy, reporting of results.

Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (OS). The results of risk of bias assessment will be reported in narrative form and in a table.

All studies will be included in the main analysis, regardless of their methodological quality. Studies will be considered at low risk of bias if study confounding, statistical analysis, prognostic factor, and outcome measurement are at low risk of bias, and participation and attrition are not at high risk of bias. In case of meta-analyses including both low- and high-risk of bias studies, the authors will perform a second meta-analysis restricted to studies with a low risk of bias as a sensitivity analysis.

Data extraction

Data will be extracted from included studies by two independent reviewers (JSR, PG) using a standardized, pre-piloted form. Extracted data will include the elements from the checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies, adapted for studies on prognostic factor (CHARMS-PF).[27] The following information will be collected:

- source of data: author, year, journal, study design, and settings;
- participants: selection process, inclusion and exclusion criteria, country and inclusion period of the study, number of patients evaluated and included, distribution of major confounders: age, sex, and hemoglobin genotype in the population;
- psychosocial prognostic factors: type, definition and measurement method, distribution in the studied population, duration when available;
- outcomes of interest: type, definition and measurement method, distribution of outcome events in the studied population (rate, count and percentage, mean or median and standard deviation, interquartile range or confidence interval depending on availability);
- analysis: number of patients with missing data, confounders included in the analysis, modeling method;
- results: adjusted and unadjusted prognostic effect estimates with their associated confidence interval for each prognostic factor of interest and outcome;
- risk of bias assessment items of the QUIPS tool.

Any disagreement between the reviewers will be resolved through discussion or with a third reviewer

(OS). Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

The authors expect multiple psychosocial risk factors, multiple measurement tools for the same exposure concept, and different measurements of emergency hospital utilization. Studies reporting the effect of the same exposure on the same outcome will be pooled with statistical meta-analysis using the R environment (R Foundation for Statistical Computing, Vienna, Austria). The authors will pool estimates for studies where the methods of measurement of risk factors and outcomes are identical or used compatible scales or instruments.[27,28] Effect sizes will be expressed as relative risk ratio or odds ratios (for dichotomous data), standardized mean differences (for continuous data), or hazard ratio (for survival data), with their 95% confidence intervals.

When available, the prognostic value of each studied risk factor will be reported unadjusted and adjusted at least for age and sex. Statistical heterogeneity will be assessed using the χ^2 test and its magnitude will be measured using the I^2 index. In the absence of significant heterogeneity, a meta-analysis will be performed and pooled statistics provided. Statistical analyses will be performed using random effect models, except when less than five studies are pooled.[29] In this case, a fixed effect model will be used, provided there is no clinical, methodological, or statistical heterogeneity between studies.

Stratified meta-analyses will be used to explore heterogeneity in effect estimates according to risk of bias. In the event of important sample size differences between included studies, the authors will perform a leave-one-out sensitivity analysis. Subgroup analyses will be conducted where there is sufficient data to differentiate adults and children, males and females, different hemoglobin genotypes, and different health care systems. Health care systems will be distinguished according to the two indicators of the World Health Organization Universal Health Coverage: the service coverage index and the incidence of catastrophic health spending (both deducted from the location and date of the study). Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated to assess publication bias if there are five or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger's test, Begg's test, Harbord's test) will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence adapted for systematic reviews of prognostic factors will be used.[30] The Summary of Findings (SoF) will present the following information where appropriate: estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, consistency, precision, and risk of publication bias of the review results, and the existence or not of a large effect or a dose response gradient. The outcomes reported in the SoF will be the risk of global emergency hospital visits, emergency department visits, emergency hospitalizations in medical wards, and emergency hospitalizations in intensive care units.

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Appendix I: Search strategy

MEDLINE/PMC (PubMed)

Search	Query	Records retrieved
#1	"Anemia, Sickle Cell"[Majr] OR ("sickle cell" AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]))	21,723
#2	"hospitalization"[tw] OR "hospitalisation"[tw] OR "hospitalization"[MeSH]	326,115
#3	("hospital*"[MeSH] OR "emergency*"[tw] OR "emergencies"[tw] OR "emergencies"[MeSH] OR "Emergency Medical Services"[MeSH]) AND ("visit*"[tw] OR "utilization*"[tw] OR "utilisation*"[tw] OR "use"[tw] OR "admission"[tw] OR "readmission"[tw] OR "Patient Admission"[MeSH] OR "Patient Readmission"[MeSH])	319,923
#4	(hospital OR emergency) AND (visit OR visits OR utilization OR utilisation OR use OR admission OR readmission) AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])	178,095
#5	#2 OR #3 OR #4	670,908
#6	"mental"[tw] OR "behavio*"[tw] OR "psychi*"[tw] OR "psychol*"[tw] OR "psychos*"[tw] OR "mood"[tw] OR "affective"[tw] OR "depressi*"[tw] OR "bipolar"[tw] OR "psychotic"[tw] OR "schizophr*"[tw] OR "schizotypal"[tw] OR "delusional"[tw] OR "anxiety"[tw] OR "anxious"[tw] OR "emotional"[tw] OR "phobic"[tw] OR "stress"[tw] OR "personality"[tw] OR "abuse"[tw] OR "addiction"[tw] OR "alcohol"[tw] OR "cannabis"[tw] OR "nicotine"[tw] OR "cocaine"[tw] OR "stimulant"[tw] OR "substance"[tw] OR "hypnotic"[tw] OR "hyperactivity"[tw] OR "adaptation"[tw] OR "neurodevelopmental"[tw] OR "somatoform"[tw] OR "Mental Disorders"[MeSH] OR "Mental Health"[MeSH] OR "Behavior"[MeSH] OR "Anxiety"[MeSH] OR "Personality"[MeSH] OR "Ethanol"[MeSH] OR "Cannabis" [MeSH] OR "Nicotine"[MeSH] OR "Cocaine" [MeSH] OR "Central Nervous System Stimulants"[MeSH] OR "Hypnotics and Sedatives"[MeSH] OR "Adaptation, Psychological"[MeSH] OR "Neurodevelopmental disorders"[MeSH] OR "Somatoform disorders"[MeSH] OR "Substance-Related Disorders"[MeSH]	5,641,085
#7	"socia*"[tw] OR "sociol*"[tw] OR "socioe*"[tw] OR "socio*eco*"[tw] OR "occupat*"[tw] OR "employment*"[tw] OR "education*"[tw] OR "literacy"[tw] OR "literate"[tw] OR "income*"[tw] OR "sociod*"[tw] OR "socio*demograph*"[tw] OR "depriv*"[tw] OR "under privileg*"[tw] OR "underprivileg*"[tw] OR "poverty"[tw] OR "precarity"[tw] OR "inequalit*"[tw] OR "inequit*"[tw] OR "disparit*"[tw] OR "welfare*"[tw] OR "insurance*"[tw] OR "insurance *"[tw] OR "medicaid*"[tw] OR "medicare"[tw] OR "cover"[tw] OR "residence"[tw] OR "post* code"[tw] OR "neighbor*"[tw] OR "neighbour*"[tw] OR "distance*"[tw] OR "homeless"[tw] OR "housing"[tw] OR "criminal*"[tw] OR "violence"[tw] OR "neglect"[tw] OR "cultur*"[tw] OR "family"[tw] OR "Parent-Child Relations"[tw] OR "Sociological Factors"[MeSH] OR "Social Medicine"[MeSH] OR "Socioeconomic Factors"[MeSH] OR "Social Class"[MeSH] OR "employment"[MeSH] OR "education"[MeSH] OR "Educational Status"[MeSH] OR "literacy"[MeSH] OR "income"[MeSH] OR "poverty"[MeSH] OR "Insurance"[MeSH] OR "Medicaid"[MeSH] OR "medicare"[MeSH] OR "Residence Characteristics"[MeSH] OR "Homeless Persons"[MeSH] OR "Housing"[MeSH] OR "Violence"[MeSH] OR "Family"[MeSH] OR "Parent-Child Relations"[MeSH] OR "Parents/education"[Mesh]	5,612,291
#8	#6 OR #7	9,408,059
#9	#1 AND #5 AND #8	533
All PubMed-accessed databases. From databases inception; no language restriction. Search conducted on 2020-05-29.		