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Risk factors for malignant transformation of hepatocellular adenoma to hepatocellular carcinoma: protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Hepatocellular adenomas (HCAs) are solid liver tumours that are usually found incidentally during routine medical check-ups. Multiple modifiable and non-modifiable factors constitute a risk for the malignant transformation of HCAs to hepatocellular carcinoma (HCC), which has emerged to be one of the fastest growing causes of cancer-related mortality globally. This study protocol for a planned systematic review and meta-analysis documents the methodological approach to identify risk factors and their risk estimates for the transformation from HCA to HCC.

Methods and analysis Two independent reviewers will systematically search and extract data from studies in patients of all ages published between January 1970 and June 2021 on PubMed, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Scopus Web of Science, Ovid, The Cochrane Hepatobiliary Group Controlled Trials Register and The Cochrane Central Register of Controlled Trials by using an *a priori* defined search strategy. Study quality will be rated with the National Institute of Health quality assessment tools. Disagreements will be resolved by consensus with a third independent reviewer. The primary outcome will be the odds ratio (OR) of developing HCC in patients with prediagnosed HCA depending on the exposure to risk factors. HCC diagnosis must be inferred based on imaging techniques or pathology. We will use R V.4.0.2 to conduct meta-analyses and generate pooled ORs based on random effects models. Results will be presented as forest plots. Cochran's Q and I^2 test will be performed to assess heterogeneity between included studies. Funnel plots and Egger's weighted regression will be used to evaluate publication bias.

Ethics and dissemination No ethical approval is required as we will use and analyse data from previously published studies in which informed consent was obtained. The results will be disseminated in a peer-reviewed journal on completion.

PROSPERO registration number CRD42020206578.

Strengths and limitations of this study

- Despite the global rise in liver cancer-related mortality and the potential of hepatocellular adenoma (HCA) for malignant transformation, management strategies for HCA are vaguely defined with regards to conservative versus surgical management based on patient risk factors.
- To the best of our knowledge, this is the first meta-analysis on identifying risk factors as well as their risk estimates for malignant transformation from HCA to hepatocellular carcinoma.
- This extensive systematic review and meta-analysis will include publications from 1970 to 2021, which will be reviewed and rated by three independent reviewers according to established quality assessment instruments.
- Malignant transformation from HCA to hepatocellular carcinoma may not be subjected to a single risk factor (eg, tumour size)—multifactorial carcinogenesis, including genetic mutations, is more likely.

INTRODUCTION

Epidemiology of hepatocellular adenoma

Hepatocellular adenomas (HCAs) are benign, solid liver tumours that are usually asymptomatic and found incidentally during routine medical check-ups. Being presumably first characterised by Frerichs in 1861,[1] HCAs have gained wide recognition since the 1960s and 1970s with the introduction of oral contraceptive pills (OCPs), one of the most established risk factors for HCA tumourigenesis in women of childbearing age[2–4] The annual incidence of HCA in women with prolonged OCP intake is approximately 3–4 per 100 000 OCP users.[5] The understanding of HCA risk factors has evolved gradually, which include demographic factors (eg, male sex), environmental factors (eg, anabolic steroid intake, obesity or metabolic syndrome), underlying liver diseases or genetic syndromes, such as glycogen storage diseases or familial adenomatous polyposis.

Malignant transformation to hepatocellular carcinoma

Given their potential for malignant transformation (hepatocellular carcinogenesis), HCAs constitute a risk for developing hepatocellular carcinoma (HCC) or haemorrhage,

which may be accompanied by abdominal pain, distension or displacement of surrounding structures. Malignant transformation to HCC has been reported in 4.2% of patients with HCA.[5]

Multiple risk factors for the transformation to HCC have been identified,[1 5] such as male sex, progression of HCA size, exogenous androgen or oestrogen intake, as well as genetic predispositions, such as mutations in b-catenin gene, hepatocyte nuclear factor 1 alpha gene or glycogen storage diseases.

On a global scale, liver cancer has become one of the fastest growing causes of cancer-related death,[6] with a 43% increase in mortality rate in the USA between 2000 and 2016.[7] As of 2018, HCC was the sixth most commonly diagnosed cancer in both sexes worldwide, as well as the second most common cause of cancer-related mortality.[8]

Rationale for systematic review and meta-analysis

Despite the aforementioned global trend[6–8] and HCA's potential for malignant transformation, management strategies for HCA are vaguely defined. Management strategies include liver resection vs conservative therapy (ie, life style change and wait and watch). There appears to be one systematic review from 2010 evaluating the risk factors for malignant transformation from HCA to HCC to the best of our knowledge.[5] Since then, numerous studies have been published on risk factors for the transformation from HCA to HCC, in particular including HCA molecular subtypes and genetic mutations.[9–13] Further, there appears to be an evidence gap for the quantitative risk assessment for the malignant transformation from HCA to HCC based on patients' underlying risk factors.

In fact, sex and size of HCA remain the most well-established parameters for treatment decisions in accordance with the guidelines of *The European Association for the Study of the Liver*. Elective liver resection is recommended in all men, while women are subjected to surgery when HCA diameter is greater than 5 cm and/or size has been progressing despite life-style changes.[14 15] Nonetheless, multiple cases reports showed malignant transformation in HCAs with diameters <5 cm, while other studies suggest an elective surgery for diameters >4 or >8 cm, opening a debate for clear cut-off values for surgical treatment.[1 16–18] Selected patients obviously benefit from a conservative therapy, such as the cessation of exogenous hormone intake, while others may benefit from surgery.[19 20]

Therefore, the aim of this study protocol is a systematic review to provide the latest overview on modifiable (eg, exogenous intake of oestrogens or androgens) and non-modifiable risk factors (eg, sex, genetic mutations or molecular subtypes of HCA) for the malignant transformation from HCA to HCC in patients of all ages. If different molecular subtypes are present in the same patient, we will include the patient in subgroups for each given molecular subtype. In addition, we aim to conduct a meta-analysis to provide risk estimates for the transformation from HCA to HCC in patients who have been exposed to a risk factor—in comparison to patients without exposure to the same risk factor.

By assessing which patient with HCA harbours the highest risk for HCC genesis, our data may support risk factor-adjusted patient management and therapy (surgery vs surveillance)—with the overall aim to improve patient outcomes and prevent malignant transformation.

METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis between June 2021 and October 2021. The development of the study design, study conduct and reporting of results will be in accordance to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA) (see online supplemental material 1) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[21 22]

Objectives

To conduct a systematic review and meta-analysis to investigate modifiable and non-modifiable risk factors of HCA, as well as their risk estimate for the malignant transformation to HCC for patients of all ages in the published literature.

Study questions

- The systematic review will address the following question: What are modifiable and non-modifiable risk factors for the malignant transformation of HCA to HCC in the literature published from 1970 to 2021?
- The meta-analysis will address the following question: What is the quantitative risk estimate for the malignant transformation of HCA to HCC in patients who have been exposed to a specific risk factor—compared with patients without exposure to the same risk factor?

Eligibility criteria

Inclusion and exclusion criteria are defined as follows (see figure 1 for PRISMA flow diagram):

Inclusion criteria

- Randomised controlled trials, observational studies (ie, cross-sectional, case–control or cohort studies with a prospective or retrospective study design) and case reports, which reported the frequency of malignant transformation from HCA to HCC in adults and non-adults.
- HCA and HCC were diagnosed based on imaging techniques or pathology according to recommendations by the *European Association for the Study of the Liver*.[14 15]
- Studies were published in English or German language from 1 January 1970 to 1 June 2021, regardless of the country or ethnic background of the study population. We selected this time period as the first known reports were published in the 1970s.

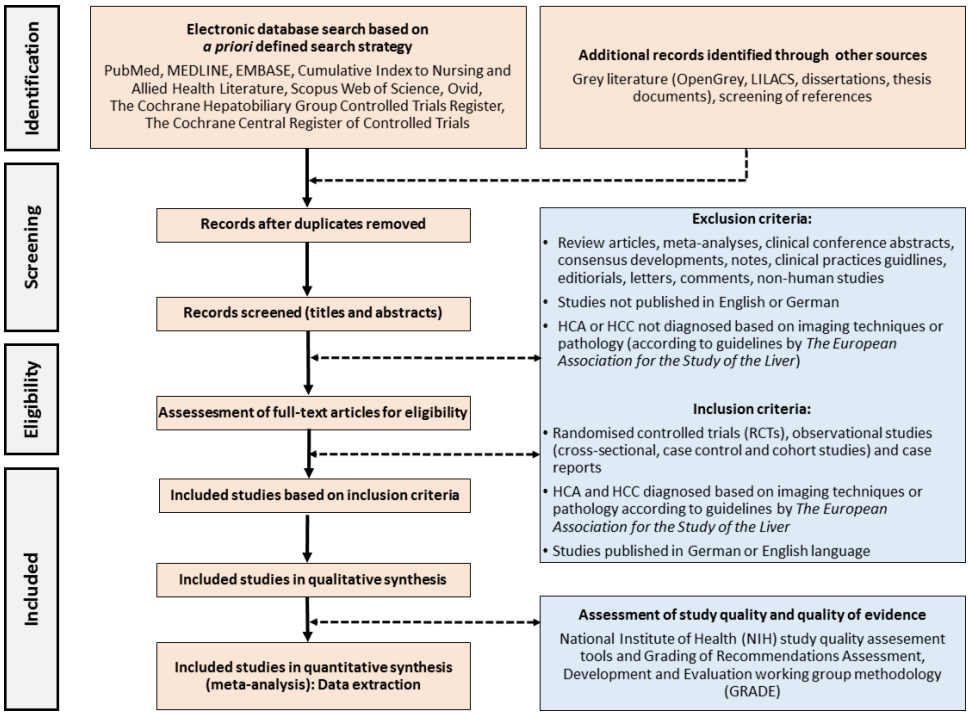

Figure 1 PRISMA flow diagram for systematic review and meta-analysis on malignant transformation from hepatocellular adenoma (HCA) to hepatocellular carcinoma (HCC). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- In case of multiple publications of the same data, we will consider the most comprehensive, recent and inclusive study.

Exclusion criteria

- (Systematic) review articles and meta-analyses to allow for an independent literature review without a study selection bias.
- Clinical conference abstracts, consensus development, notes, clinical practice guidelines, editorials, letters and comments.
- Studies with unclear reporting of risk estimates for malignant transformation from HCA to HCC.
- Studies in which HCA and HCC were not diagnosed based on imaging techniques or pathology according to recommendations by the *European Association for the Study of the Liver*.[14 15]
- Non-human studies.
- Studies were not published in English or German.

Search strategy

We will conduct a comprehensive literature search to identify relevant studies according to our aforementioned eligibility criteria. We will perform a systematic search on PubMed, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus Web of Science, Ovid, The Cochrane Hepatobiliary Group Controlled Trials Register and The Cochrane Central Register of Controlled Trials (CENTRAL) by using an a priori defined search strategy based on a combination of keywords of our research question: 'hepatocellular adenoma' and 'patients'. In contrast to a previously published systematic review,[5] we will not include the keywords 'malignant transformation' or 'liver resection' to allow for a more open search approach. For grey literature, we will use OpenGrey, LILACS, dissertations or thesis documents.

We will conduct the search based on principles of Boolean operators (AND, OR and NOT), incorporate free-text words and Medical Subject Headings, as well as different versions of medical terminology. We will use the following search strategy on PubMed:

("hepatic" OR "liver" OR "liver cell" or "hepatocellular") AND ("adenoma" or "hepatoma") AND ("patient") NOT (meta-analysis[Filter]) NOT (review[Filter]) NOT (systematicreview[Filter]) NOT (comment[Filter]) NOT (congress[Filter]) NOT (consensusdevelopment-conference[Filter]) NOT (consensusdevelopment-conferencenih[Filter]) NOT (editorial[Filter]) NOT (guideline[Filter]) NOT (letter[Filter]) AND (humans[-Filter]) AND (english[Filter] OR german[Filter]) AND (1970:2021[pdat])

Study selection

Reviewer A will apply the search strategy across all aforementioned electronic platforms and compile a list of retrieved titles in Microsoft Excel. Independent investigators B and C will review the listed publications by screening their titles and abstracts for eligibility criteria. After screening, the full text of all eligible studies deemed relevant will be retrieved and again independently reviewed deliberately by reviewers B and C to ascertain eligibility. In case of disagreement, consensus will be obtained by

$$\text{Odds ratio} = \frac{\left(\frac{a}{b}\right)}{\left(\frac{c}{d}\right)}$$

		HCC in patients with pre-diagnosed HCA	
		Yes (Case)	No (Control)
Exposure to risk factor	Yes	a	b
	No	c	d

Figure 2 Calculation of ORs of developing hepatocellular carcinoma (HCC) in patients with prediagnosed hepatocellular adenoma (HCA) based on exposure to risk factors.

reviewer A. In addition, B and C will complement the database search by manually reviewing the reference lists of all included publications to include publications that may have not been identified by the search strategy.

Data extraction and management

Two data extractors will independently extract the data from all included studies by using a standardised data collection form which will be created by a third reviewer. The following data will be extracted: authors, year, country, study design, setting, sample size, risk factor, frequency of HCC in HCA patients with exposure to a risk factor, frequency of HCC in HCA patients without exposure to a risk factor, frequency without HCC in HCA patients with exposure to a risk factor, frequency without HCC in HCA patients without exposure to a risk factor (see paragraph on the section 'Primary Outcome'). Inter-rater agreement between the two data extractors will be analysed using kappa statistics.[23]

If the frequency of HCA or HCC is not reported, we will calculate the frequency using the study sample size and the number of outcomes. In studies where HCC incidence is reported in two or more arms, each study arm will be considered as a single study. In this case, we will extract the data from each study arm separately.

Missing outcome data

In case of missing outcome data, we will contact the corresponding study authors. We will perform sensitivity analyses to assess the robustness of the meta-analysis and discuss the impact of missing data on the findings. We will not apply statistical approaches (eg, data imputation, analysis of worst and best cases) to adjust for missing

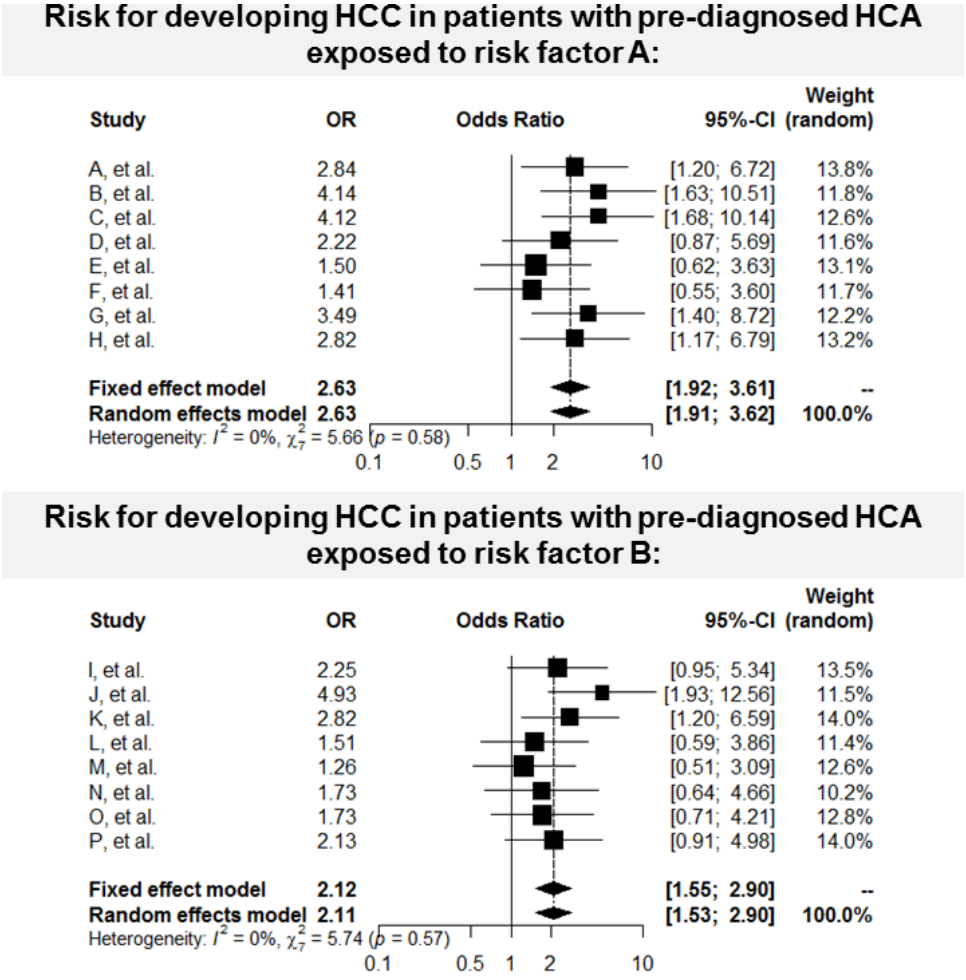

Figure 3 Planned meta-analyses (based on sample data as an example) on risks of developing hepatocellular carcinoma (HCC) in patients with prediagnosed hepatocellular adenoma (HCA) depending on exposure to risk factors.

outcome data as these are considered to be not effective and less recommended in meta-analyses.[24]

Methodological study quality and quality of evidence

The methodological quality (risk of bias) of the included interventional and observational studies will be rated by two independent reviewers as good, fair and poor by incorporating the National Institute of Health quality assessment tools.[25] Additionally, the strength of the body of evidence will be rated as very low, low, moderate and high by using the Grading of Recommendations Assessment, Development and Evaluation working group methodology.[26] We will assess the quality of evidence across the domains of risk of bias, consistency, directness, precision and publication bias.

Primary outcome

The primary outcome of our meta-analysis will be the OR of developing HCC in HCA patients based on as to whether the patients were exposed to a risk factor. Diagnosis of HCC must be inferred based on imaging techniques or pathology.[15] We will collect the following information to calculate the odds ratio (see figure 2):

1. Number of HCA patients who were exposed to a risk factor and have developed HCC.
2. Number of HCA patients who were exposed to a risk factor and have not developed HCC.
3. Number of HCA patients who were not exposed to a risk factor and have developed HCC.
4. Number of HCA patients who were not exposed to a risk factor and have not developed HCC.

Data synthesis, results presentation and statistical analyses

Number of included and excluded search results will be presented in a PRISMA flow diagram, including the rationale for study exclusion (see figure 1).[27] Included studies will be presented in an evidence table and summarised by using descriptive statistics. For studies that are not eligible for quantitative synthesis, we will provide a narrative synthesis with information being presented in the text and/or a table to summarise and explain the characteristics and findings.

We will use R V.4.0.2 (R Core Team 2020. Vienna, Austria) to conduct the meta-analyses and generate a pooled risk estimate of the overall OR for developing in HCC in patients with prediagnosed HCA depending on exposure to risk factors (see figure 3).

Study heterogeneity

We will assess the study heterogeneity between publications by using the Cochran's Q test and I^2 statistics. We will define heterogeneity as low, moderate and high in accordance to values below 25%, between 25% and 75% and above 75%, respectively. We will apply random effects models to account for heterogeneity in meta-analyses, as well as random effects meta-regression analysis to examine the sources of heterogeneity.

Subgroup analyses and cumulative meta-analysis

We will conduct subgroup analyses based on different HCA diameters, study quality (high-quality vs low-quality studies) and time period (prior to 2000 vs post-2000). With an exploratory intent, we will perform a cumulative meta-analysis to identify the time point at which the risk factors first reached conventional levels of significance.

Publication bias

We will use funnel plots and Egger's weighted regression to assess publication bias. In case of existing publication bias, we will perform Duval and Tweedie non-parametric 'trim-and-fill' analyses.

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Contributors TT, TC, MS, JP and FK have made substantial contributions to the conception and design of the planned systematic review and meta-analysis, as well as have written, critically revised and approved the study protocol. FK is the guarantor of the systematic review and meta-analysis. All authors meet the ICMJE criteria for authorship.

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