Thematic Miniseries on
NAFLD-derived HCC

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Rational HCC screening approaches for patients with NAFLD

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Summary

Non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of developing hepatocellular carcinoma (HCC), especially among those who have cirrhosis or advanced fibrosis, but 20–30% of cases of NAFLD-related HCC occur in the absence of advanced fibrosis. The prevalence of NAFLD-related HCC is increasing in most countries worldwide. There are few direct data to support or refute the efficacy or effectiveness of HCC surveillance in NAFLD or to guide its application. We use evidence on surveillance in other conditions and studies on the clinical course of patients with NAFLD to arrive at recommendations for rational approaches to HCC surveillance in this growing cohort of patients. We also outline gaps in research and practice, including opportunities to advance the field.

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Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide, with increasing mortality rates in several parts of the Western world.[1,2] The prognosis of HCC is generally dismal except in patients who are diagnosed at an early stage and receive curative treatment. Therefore, HCC surveillance is commonly recommended in high-risk patients to increase the proportion of patients detected at an early stage. Contemporary epidemiological observations indicate a shift in the aetiology of cirrhosis and HCC from viral hepatitis to non-alcoholic fatty liver disease (NAFLD).[3,4] Herein, we discuss the evidence supporting these recommendations and rational approaches to HCC surveillance in current clinical practice.

Evidence supporting HCC surveillance

Several professional societies recommend HCC surveillance in high-risk individuals, including subgroups of patients with chronic HBV infection and those with cirrhosis of any aetiology.[5,6] There are only limited level I data from randomised clinical trials (RCTs) to support HCC surveillance. An RCT conducted in China in the 1990s among 18,920 patients with HBV infection[7] reported significantly increased early tumour detection and curative treatment receipt in patients randomised to surveillance with ultrasound and alpha-fetoprotein (AFP) compared with those who were not screened for HCC, resulting in a 37% reduction in HCC-related mortality. It is unclear whether the survival benefit would have persisted if the analytical plan adhered to intention-to-treat principles or accounted for block randomisation.[8] It is also unclear if these data apply to patients with NAFLD-related cirrhosis, for several reasons: i) increased liver nodularity in the setting of cirrhosis may impair the effectiveness of ultrasound to detect HCC nodules at an early stage, ii) a higher prevalence of obesity among patients with non-alcoholic steatohepatitis (NASH) may further impair ultrasound performance, and iii) an increased risk of liver- and non-liver-related mortality in patients with NAFLD-related cirrhosis, compared to non-cirrhotic hepatitis B infection, may mitigate surveillance-related survival benefits. Subsequent RCTs among patients with cirrhosis were either too small and underpowered[9] or terminated given poor enrolment because patients did not accept being randomised to the no surveillance arm.[10] Hence, surveillance recommendations in patients with cirrhosis are based on level II observational cohort data. A systematic review of 47 studies, most of which were retrospective (n = 42), demonstrated that HCC surveillance is associated with increased tumour detection (odds ratio [OR] 2.08; 95% CI 1.80–2.37), increased receipt of curative treatment (OR 2.24; 95% CI 1.99–2.52) and improved 3-year survival (OR 1.90; 95% CI 1.67–2.17).[11,12] Observational studies may overestimate benefit due to inherent biases, however, surveillance remained associated with improved survival in the subset of studies adjusting for lead time bias and length time bias.[12] However, studies in this systematic review were mostly conducted among patients with viral hepatitis, with no studies specifically examining patients with NAFLD-related cirrhosis. Observational studies may also underestimate the efficacy of HCC surveillance because of a lack rigorous implementation, which can lead to delays in the diagnosis and treatment of HCC. Some contemporary data suggest HCC surveillance may not be of benefit in patients with cirrhosis, with a nested case-control study from the Veterans Affairs Health System failing to find an

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Key point

Several cohort studies and decision analyses suggest that HCC surveillance is associated with increased early HCC detection and reduced HCC-related mortality in patients with cirrhosis, although specific data in patients with NAFLD are lacking.

association between receipt of surveillance and improved survival,[11] although the retrospective nationwide practice-based observational setting was inevitably associated with delays in diagnosis and treatment of HCC that would reduce the effectiveness of HCC surveillance.[13] Overall, the available studies provide a moderately strong rationale for HCC surveillance in patients with chronic HBV or cirrhosis in general but contain little specific information for or against HCC surveillance in NAFLD or NAFLD-related cirrhosis. Future studies are needed to address this gap in the literature, particularly given the rising burden of NAFLD-related cirrhosis and HCC.[4]

Cost-effectiveness of HCC surveillance

Assuming that HCC surveillance is effective in reducing HCC-related mortality, several decision analysis models have suggested that surveillance is cost effective in patients with compensated cirrhosis.[14–19] The decision to enter a patient into an HCC screening programme, irrespective of the aetiology of cirrhosis, is determined based on cost-effectiveness considerations including the level of HCC risk, competing risk of non-HCC mortality, the patient's ability to comply with screening recommendations and treatment candidacy if found to have HCC. Several studies demonstrate that the cost of screening per quality-adjusted life year decreases with increasing HCC risk. Although HCC risk is one of the most important factors in determining the cost-effectiveness of HCC surveillance, decision analyses also found surveillance utilisation and test performance are important determinants of HCC surveillance effectiveness and ability to afford a survival benefit.[11] Cost-effectiveness analyses indicate that HCC screening should be considered for patients with Child-Pugh A cirrhosis and HCC risk exceeding 1.0–1.5% per year, with the lower end of the range reported by a more recent cost-effectiveness analysis that incorporated contemporary estimates of sensitivity and specificity of screening and the effectiveness of curative treatments.[14] Patients with cirrhosis from various aetiologies, including NAFLD and HCV following sustained virological response (SVR), typically fall in this range of annual HCC risk. The annual incidence rates of HCC in NASH-related cirrhosis cohorts range from 0.2 to 2.6%.[20] The wide variation is explained by differences in age, metabolic profile and presence or severity of hepatic decompensation in patients included in these studies. The data comes largely from either clinic- or hospital-based cohort studies, and transplant registry databases with only sparse high-quality, population-based cohort studies. A large retrospective cohort study from the national Veterans Affairs system in the United States estimated HCC risk in 296,707 patients with NAFLD: the overall annual HCC risk was 1.06% but it ranged from 0.2% in women to 2.4% in older Hispanics with cirrhosis.[18] HCC incidence rates are higher in patients with decompensated cirrhosis than in those with compensated cirrhosis, while male sex, presence of diabetes, obesity, dyslipidaemia, alcohol intake and Hispanic ethnicity (in the US) are additional risk factors for HCC in patients with NASH-related cirrhosis. Patients with F3 fibrosis, especially in the setting of NAFLD or post-SVR HCV, have an intermediate risk of developing HCC that is lower than that of patients with cirrhosis; they are also difficult to stage reliably in a non-invasive manner, making HCC surveillance decisions harder and less favourable from a cost-effectiveness standpoint. The incidence of HCC in those with NAFLD and earlier stages of fibrosis (stage 0–2) is low and determinants of risk have not been well-quantified; therefore, systematic HCC screening is not currently recommended.[21] Several studies have shown that patients with NAFLD without cirrhosis may rarely develop HCC.[22,23] While 20–30% of NAFLD-related cases of HCC occur without cirrhosis, the very large number of at-risk patients with non-cirrhotic NAFLD makes HCC surveillance impractical with current methods. Based on the annual risk of HCC, guidelines recommend that HCC surveillance be considered in patients with compensated cirrhosis and those with decompensated cirrhosis awaiting liver transplantation.[5,24] The American Gastroenterology Association Clinical Practice Update recommends that HCC screening be considered for patients with non-invasive markers that indicate the presence of advanced fibrosis (F3).[6]

Key point

HCC risk is sufficiently high to warrant HCC surveillance in patients with NAFLD-related cirrhosis but not in those with non-cirrhotic NAFLD; patients with F3 fibrosis represent a dilemma.

Favourable cost-effectiveness of HCC surveillance has primarily been demonstrated in patients with Child-Pugh A cirrhosis. Patients with worse liver dysfunction have a higher competing risk of liver-related mortality, so the survival benefit associated with early HCC detection is mitigated. Likewise, patients with significant non-hepatic comorbidity may derive less benefit from HCC surveillance given their higher risk of non-liver-related mortality. It is therefore possible that some patients with NAFLD, particularly those whose cardiovascular risk profile exceeds their HCC risk, may derive less benefit from surveillance.[25] However, these factors need to be investigated further.

Identifying patients at-risk of HCC

Risk stratification is the identification of groups based on their short- and long-term HCC risk that can either be targeted for prevention (including surveillance) or spared such intervention. Determination of cirrhosis or advanced fibrosis status has been the main risk stratifier in NAFLD and in current practice is mostly determined by non-invasive techniques. To minimise the likelihood of misclassification, one recommended approach is to combine ≥2 non-invasive fibrosis tests of separate categories (*i.e.*, blood based, imaging based). If both

Table 1. Summary of recommendation for current and future practice and research for NAFLD-related HCC.

HCC surveillance in NAFLD	Practice recommendation	Research recommendations
Why	• Mostly level 2 data in viral and alcohol-related liver disease	• Studies in NAFLD populations
Who	• NAFLD-related cirrhosis • Possible F3 fibrosis • Not in NAFLD with F0-2	• Studies in F3 fibrosis • Studies of HCC risk factors in non-cirrhotic NAFLD
How	• Biannual ultrasound and AFP • Cross-sectional imaging in select patients	• Phase III biomarker studies in NAFLD
Effectiveness	• Better diagnosis and staging of NAFLD, high-quality ultrasound or substitute with cross-sectional imaging in select patients • Better patient selection, implementation of surveillance, recall, diagnosis, treatment	• Clinical care pathways for diagnosis and stratification of NAFLD • Accurate and reliable HCC risk calculators • Identification of patients who warrant cross-sectional imaging instead of ultrasound and AFP • Implementation studies for HCC surveillance
Cost-effectiveness	• Favourable in NAFLD-related cirrhosis based on annual HCC risk	• NAFLD-specific cost-effectiveness analyses

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

tests are concordant for either advanced fibrosis or cirrhosis, this finding supports consideration of HCC surveillance. For patients without advanced fibrosis, the risk of HCC is too low to recommend screening.[26] Cohort studies in NAFLD indicate an elevated HCC risk >1% with fibrosis-4 (FIB-4) >3.25 irrespective of the mention or diagnosis of cirrhosis; thus, these patients could be considered for HCC surveillance.[21] Similarly, multiple studies in patients with NAFLD and/or NASH show that liver stiffness is independently associated with HCC risk. Patients with NAFLD but without advanced fibrosis or cirrhosis (based on a combination of the FIB-4 test and fibroscan) should not be offered surveillance.

Multivariable HCC risk calculators have been developed to estimate HCC risk (*i.e.*, risk stratification) in individual patients with NAFLD. However, none of these calculators are ready to guide HCC surveillance decisions in clinical practice, owing to the lack of external validation in some, modest performance in others and a lack of testing for the specific purpose of HCC risk stratification. One such model was developed using Veterans Affairs datasets and includes age, gender, diabetes, BMI, platelet count, serum albumin and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio and was reported to have a c-statistic of 0.75 but has not been validated outside the Veterans Affairs.[27] The Veterans Affairs score is similar in composition to the NAFLD fibrosis score, which contains age, BMI, diabetes, AST, ALT, platelets and albumin and had a reported c-index of up to 0.9[28] in a study of 1,173 European patients with NAFLD, in whom only 17 HCC cases developed. Another model incorporated genetic variants in *PNPLA3-TM6SF2-GCKR-MBOAT7* and *HSD17B13* in a risk score that predicted HCC independently of classical risk factors and cirrhosis in a mostly Caucasian population, but this score had an AUROC of only 0.65. This is an important area for future research (Table 1).

Choice of HCC surveillance tests

The AASLD and EASL recommend semi-annual abdominal ultrasound, with or without AFP, as the primary strategy for HCC surveillance.[5,6] Abdominal ultrasound has been the primary HCC surveillance test for nearly 20 years; it has several advantages including being widely available, non-invasive, inexpensive, and safe (*e.g.* no risk of contrast or radiation exposure). Ultrasound-based surveillance is supported by the previously mentioned large RCT among HBV-infected individuals, as well as by several cohort studies.[7,12] However, recent data have highlighted limitations of ultrasound-based surveillance, including its operator-dependent nature, with high variability in performance between centres, limited sensitivity to detect HCC at an early stage if used alone without AFP, and risk of screening-related harms.[29–31] Increasing data also suggest that ultrasound visualisation may be inadequate for the exclusion of liver lesions in approximately one-fifth of patients undergoing surveillance, with the greatest risk in patients with obesity and those with non-viral aetiologies of cirrhosis including NAFLD. For example, a study of 941 patients with cirrhosis who underwent ultrasound reported that 20% of the scans were of inadequate quality to exclude liver lesions.[32] NASH-related cirrhosis and elevated BMI were 2 factors associated with inadequate scan quality. Poor visualisation can contribute to poor sensitivity for early-stage HCC detection, with a recent meta-analysis reporting a pooled sensitivity for ultrasound alone of only 45%, as well as increased risk of false positive or indeterminate surveillance results, resulting in additional diagnostic imaging, cost, and harm.[29,31] Liver visualisation by ultrasound may be improved by

Key point

The effectiveness of HCC surveillance to reduce mortality is driven by implementation in practice and sufficient test accuracy.

systematic documentation and scoring, and if found to be inadequate, MRI or CT scans should be considered instead.[33,34] Although improved visualisation can be obtained by using repeat ultrasound exams, patients with NAFLD have increased odds of persistent poor visualisation; thus, alternative surveillance imaging modalities, such as MRI, may be warranted in these patients.[30] Finally, abdominal ultrasound may require a separate radiology appointment in some countries (*e.g.*, the United States), which can reduce adherence and negatively impact the effectiveness of surveillance given patient-reported scheduling and transportation barriers.[35]

Professional society guidelines differ in their recommendations about the utility of using AFP in combination with ultrasound for HCC surveillance. Although the AASLD guidelines recommend abdominal ultrasound with or without AFP, EASL guidelines endorse ultrasound alone. AFP has several of the same advantages as ultrasound, as it is inexpensive and widely available; however, its limited sensitivity to detect early-stage HCC has historically hampered enthusiasm for its widespread use. The aforementioned meta-analysis found that AFP is likely of additional benefit when combined with ultrasound, with sensitivity for early-stage HCC detection increasing from 45% with ultrasound alone to 63% with the 2 tests in combination.[29] Although this benefit was associated with a small drop in specificity, the diagnostic OR (which factors in both sensitivity and specificity) for the 2 tests in combination was higher than that of ultrasound alone. Considering ultrasound's increased limitations in those with obesity and NAFLD-related liver disease, AFP may have an even greater additive value in this population compared to historic cohorts in which many patients had active viremia and were prone to frequent false positive AFP results. Notably, physical harms of AFP, *i.e.* additional diagnostic evaluation due to false positive or indeterminate results, are often mitigated in clinical practice as providers follow biomarker trends when interpreting AFP values instead of strictly using a single-measurement threshold of 20 ng/ml.[31] Tayob and colleagues have demonstrated that using longitudinal biomarker data, instead of a single threshold assessment, significantly increases biomarker performance.[35,36] The HCC early detection strategy (HEDS), which combines AFP with ALT, platelet count and optional previous AFP value and underlying aetiology (HCV, HBV, alcohol-related liver disease), was validated in retrospective cohort studies and shown to increase sensitivity 5–10% over AFP alone.[36–38]

Considering tumour heterogeneity, a single biomarker is unlikely to be of sufficient accuracy for early-stage HCC detection. Other blood-based biomarkers, such as lectin-bound AFP (AFP-L3%) and des-gamma carboxyprothrombin (DCP) are commonly used in some regions like Japan and are under investigation in other places. There has been increased interest in early detection biomarker panels that use multiple biomarkers, and in combining demographic and clinical variables with blood-based biomarkers. For example, GALAD, a panel that combines gender, age, AFP, AFP-L3%, and DCP, has been evaluated in a multinational case-control study, wherein it had a sensitivity of 60–80% for detecting early-stage HCC.[39] This panel was also recently evaluated in a case-control study of patients with NAFLD and was found to have a similar diagnostic performance at a cut-off of -0.63, with a sensitivity and specificity of 68% and 95%, respectively, for early-stage HCC.[40] However, most early detection biomarkers, including GALAD, have only been evaluated in phase II (case-control studies) biomarker studies and still require validation in phase III and phase IV (cohort) studies prior to recommending routine adoption.[41] In addition, the increase in sensitivity that comes with the additional use of AFP L3, DCP or GALAD also comes with a decrease in specificity (*i.e.*, increased false positive tests), which adds to the expense and harms of surveillance and must be examined in cost-effectiveness analyses. The maturation of large prospective cohort studies, such as the Early Detection Research Network's HEDS study and the Texas HCC Consortium study[42,43] will soon facilitate phase III evaluation (*i.e.*, prospective specimen collection, retrospective blinded evaluation in cohort studies) of several biomarkers (Table 1).

With advances in genomics, dysregulated nucleic acids have increasingly been identified and could potentially serve as surveillance biomarkers. DNA abnormalities isolated from circulating tumour cells and quantitative analysis of cell-free DNA have shown moderate sensitivity for detecting HCC. A methylated DNA marker panel was shown to have promising accuracy in a phase II biomarker study, with sensitivity and specificity for early HCC detection of 70% and 89%, respectively.[44] However, these biomarkers still require validation in large cohort studies using standardized processing techniques and cut-offs. While awaiting these data for both protein and cell-free DNA biomarkers, AFP is the only biomarker for which all 5 phases of biomarker evaluation have been completed and for which there is sufficient evidence for its use in clinical practice (in combination with ultrasound).

Cross-sectional abdominal imaging is increasingly used for HCC surveillance in clinical practice, although this practice is supported by limited data. CT-based surveillance is limited by concerns of repeated radiation exposure and risk of contrast injury; however, an MRI-based strategy does not have the same limitations. The PRIUS study, a prospective cohort study from South Korea, compared MRI- and ultrasound-based surveillance

Key point

HCC surveillance is underused in clinical practice, highlighting the need for interventions to better identify at-risk individuals and promote HCC surveillance completion.

in a cohort of 407 high-risk patients with cirrhosis and found that MRI had significantly higher sensitivity for early HCC detection (85.7% *vs.* 26.2%), as well as higher specificity (97.0% *vs.* 94.4%).[45] However, there are concerns about the cost-effectiveness of MRI, the lack of confirmatory data in non-hepatitis B patient populations including those with NAFLD, and access, particularly in areas with more limited radiologic capacity. Several case-control studies have reported on abbreviated MRI protocols, which decrease in-scanner time to one-third of that used for a full diagnostic MRI while preserving high sensitivity for early HCC detection; however, these data still need to be confirmed in larger cohort studies prior to use in clinical practice[46] (Table 1). At this time, ultrasound remains the primary imaging modality for HCC surveillance, with MRI reserved for select patients in whom ultrasound visualisation is reported to be inadequate.

HCC surveillance intervals

HCC surveillance is recommended at semi-annual intervals based on an HCC tumour doubling time of approximately 5–6 months as well as observational data demonstrating superiority of a semi-annual surveillance interval to annual surveillance and non-inferiority to quarterly surveillance. An analysis of 649 patients with HCC from the ITA.L.I.CA registry found that patients who had completed semi-annual surveillance were significantly more likely to be identified at an early stage (70.0% *vs.* 57.7%), undergo curative therapies (81.8% *vs.* 69.6%), and have improved survival (40.3 *vs.* 30 months) compared to those who had undergone annual surveillance.[47] A subsequent RCT in 1,278 patients with cirrhosis from France and Belgium compared quarterly and semi-annual ultrasound-based surveillance. Although quarterly surveillance detected more sub-centimetre lesions, there was no difference in the proportion of patients with HCC detected at an early stage (79.2% *vs.* 71.4%) between the groups.[48] Recent data on tumour growth patterns suggest that patients with non-viral aetiologies, including NAFLD, have longer tumour doubling times than those with viral aetiologies of cirrhosis[49,50]; however, it is unclear if these differences would translate into different surveillance intervals.

HCC surveillance implementation

For HCC surveillance to be effective in clinical practice,[51] the recognition and identification of individuals with risk factors for chronic liver disease needs to improve, as does their subsequent staging to identify those with cirrhosis and advanced fibrosis. Under-recognition of cirrhosis is greater in NAFLD than other aetiologies.[52] The effectiveness of HCC surveillance is also limited by underuse in clinical practice, with a meta-analysis reporting that less than 1 in 4 patients with cirrhosis undergo surveillance.[53] Underuse was observed across geographic areas, including North America, Europe, and Asia. Commonly reported correlates of surveillance include higher receipt among patients followed by Gastroenterology subspecialists and lower receipt among those with alcohol- or NAFLD-related cirrhosis. Multiple failures contribute to surveillance underuse, including under-recognition of at-risk individuals, providers failing to order surveillance in those with known cirrhosis, and patient non-adherence. Lower HCC surveillance in patients with NAFLD is likely related to lower recognition of cirrhosis in NAFLD compared to other aetiologies.

To ensure the effectiveness of HCC surveillance, there must also be adequate recall procedures with timely diagnostic evaluation in those with positive surveillance results, and timely guideline-concordant treatment in those who are found to have HCC.[54] Patients with a sub-centimetre nodule observed on ultrasound are typically at low risk of HCC, which is difficult to verify by further cross-sectional imaging or biopsy; the recommendation is to perform a follow-up ultrasound in 3–6 months. If a nodule demonstrates persistent stability in size and features, the patient could return to semi-annual surveillance. However, lesions ≥1 cm are associated with a higher risk of HCC; hence, contrast-enhanced MRI or multi-phase CT imaging should be performed in such cases. Unfortunately, studies have demonstrated diagnostic delays in those with positive surveillance results as well as underuse of curative treatments in those with early-stage HCC.[13] These downstream failures can mitigate, if not obviate, the survival benefit of HCC surveillance and need to be addressed in future clinical and research efforts (Table 1).

Key point

Ultrasound-based surveillance has low sensitivity for detection of HCC at an early-stage and there is increasing interest in novel blood- and imaging-based surveillance strategies; however, these require validation in large cohort studies prior to implementation in clinical practice.

Conclusion

While there is a lack of direct data to support HCC surveillance in patients with NAFLD-related cirrhosis, several cohort studies and decision analyses suggest this practice is associated with increased early HCC detection and reduced HCC-related mortality. The unique challenges of implementing surveillance among patients with NAFLD include increased difficulty recognising at-risk patients with cirrhosis, a higher proportion of patients developing HCC in the absence of cirrhosis, and a higher competing risk of non-liver-related mortality mitigating surveillance benefits compared to other liver disease aetiologies. The cost-effectiveness of HCC surveillance in NAFLD needs to be examined in greater depth. There is also increasing recognition that surveillance using ultrasound alone offers insufficient diagnostic accuracy and that novel blood- and imaging-based surveillance tests are needed. This is particularly true for patients with NAFLD, in whom ultrasound visualisation and test performance is impaired in the setting of obesity. While awaiting validation of promising novel surveillance strategies, efforts are

needed to optimise the implementation and effectiveness of semi-annual surveillance and follow-up among at-risk patients with NAFLD in clinical practice.

Abbreviations

AFP, alpha-fetoprotein; AFP-L3%, lectin-bound AFP; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-gamma carboxyprothrombin; HCC, hepatocellular carcinoma; HEDS, HCC early detection strategy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomised clinical trials; SVR, sustained virological response.

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Conflict of interest

Amit Singal has served as a consultant or on advisory boards for Bayer, FujiFilm Wako Diagnostics, Exact Sciences, Roche, Glycotest, and GRAIL. Hashem El-Serag had grant funding from Gilead, Merck, Wako and Glycotest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AS: conception, design, literature review, writing of first draft, approval of last draft; HES: conception, design, literature review, writing of first draft, approval of last draft.

Supplementary data

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