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Can biomarkers be used to improve diagnosis and prediction of metabolic syndrome in childhood cancer survivors? A systematic review

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Summary

Childhood cancer survivors (CCS) are at increased risk to develop metabolic syndrome (MetS), diabetes, and cardiovascular disease. Common criteria underestimate adiposity and possibly underdiagnose MetS, particularly after abdominal radiotherapy. A systematic literature review and meta-analysis on the diagnostic and predictive value of nine newer MetS related biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apolipoprotein B (apoB), and lipoprotein(a) [lp(a)]) in survivors and adult non-cancer survivors was performed by searching PubMed and Embase. Evidence was summarized with GRADE after risk of bias evaluation (QUADAS-2/QUIPS). Eligible studies on promising biomarkers were pooled. We identified 175 general population and five CCS studies. In the general population, valuable predictive biomarkers are uric acid, adiponectin, hsCRP and apoB (high level of evidence), and leptin (moderate level of evidence). Valuable diagnostic biomarkers are hsCRP, adiponectin, uric acid, and leptin (low, low, moderate, and high level of evidence, respectively). Meta-analysis showed OR for hyperuricemia of 2.94 (age-/sex-adjusted), OR per unit uric acid increase of 1.086 (unadjusted), and AUC for hsCRP of 0.71 (unadjusted). Uric acid, adiponectin, hsCRP, leptin, and apoB can be alternative biomarkers in the screening setting for MetS in survivors, to enhance early identification of those at high risk of subsequent complications.

KEYWORDS
biomarker, childhood cancer survivors, systematic review, the metabolic syndrome

Abbreviations: ALL, acute lymphoblastic leukemia; apoA1, apolipoprotein A1; apoB, apolipoprotein B; AUC, area under the curve; BMI, body mass index; CCS, childhood cancer survivors; CVD, cardiovascular disease; DXA, dual-energy X-ray Absorptiometry; GRADE, Grading of Recommendations Assessment Development and Evaluation; HDL, high density lipoproteins; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; IL-1, interleukin 1; IL-6, interleukin 6; LDL, low density lipoproteins; Lp(a), lipoprotein(a); MetS, metabolic syndrome; OR, odds ratio; ROC, receiver operating characteristic; T2DM, type 2 diabetes mellitus; TNF-alpha, Tumor Necrosis Factor alpha.

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1 | INTRODUCTION

Childhood cancer 5-year survival rates have increased from 5–30% in early seventies to more than 80% in the present time.[1,2] Deployed therapies, such as chemotherapy, radiotherapy, and stem cell transplantation, better stratification, and enhanced supportive care regimens, are responsible for increase in survival rates. However, intensification of treatment is also associated with long-term excess mortality and morbidities in survivors.[3] Survivors have a high level of frailty, suggesting their biological age progresses faster than their actual age. Consequently, survivors with an actual mean age of 33 have a biological age of 65 if they are compared with the general population.[4–9] At the age of 45–50 years, the prevalence of any chronic health condition is very high, from 95% up to 99%.[3,10] One of these severe conditions is represented by cardiovascular disease (CVD), which is an important cause of premature death beyond 5 years cancer survival; the standardized mortality risk for CVD ranges from 1.9 to 12.7.[11–25]

This high risk of cardiovascular death is not only due to treatment effects, such as anthracycline exposure and cardiac irradiation[26]; survivors are also at high risk of type II diabetes mellitus (T2DM) and the metabolic syndrome (MetS).[11] These diseases are independent predictors of CVD and associated with factors such as adiposity, dyslipidemia, insulin resistance, and hypertension. These factors cluster together and form the "deadly quartet," a MetS concept developed by Reaven in 1988.[27] The MetS had many definitions ever since.[11,27–37] Patients with MetS carry a doubled risk of dying from cardio- and cerebrovascular disease.[11,38] In addition, patients with the MetS are five times more likely to develop T2DM, which subsequently triples the risk of CVD.[11,39–41]

As survivors develop cardiovascular complications at a relatively young age, there is a need for early diagnosis of MetS, to possibly prevent T2DM and CVD, and to improve long-term survival.[11] The occurrence of MetS may be underestimated especially in abdominally irradiated childhood cancer survivors (CCS), who have an unreliable waist circumference, while their MetS risk is even higher.[11,42–44] Body mass index (BMI) and bioimpedance are alternative methods for body composition measurement but do not specifically measure abdominal fat, rely on hydration status, and often underestimate body fat.[42,45–47] Obviously, another alternative option to evaluate adiposity is measuring fat percentage by Dual-energy X-ray Absorptiometry (DXA) scan, which is the gold standard in case of suspected discordance of anthropomorphic measurements and adiposity.[42,48,49] However, performing DXA scans in all survivors on a routine basis is time-consuming and costly.[11] Additionally, there is currently no consensus for the threshold of fat percentage for diagnosing obesity.[50] Newer serum biomarkers may serve as another alternative for accurate early diagnosis or prediction of (disguised) MetS in CCS. Adult cardiologists currently apply multiple biomarkers that have been shown to improve risk estimation for CVD.[51]

Therefore, our primary objectives were to evaluate the value of the use of these newer serum biomarkers as (1) diagnostic marker and as (2) additional independent predictor for the occurrence of MetS later in life, in survivors of childhood cancer specifically, and in a relatively young general, non-cancer population (studies with >75% of participants below 65 years). By including this selection of general population studies as well, we aimed to cover all available literature applicable and generalizable to young-adult survivors. To accomplish this, we performed a systematic literature search on adipokines adiponectin and leptin, uric acid, the inflammatory markers high sensitivity C-reactive protein (hsCRP), Tumor Necrosis Factor alpha (TNF-alpha), interleukin 1 (IL-1) and interleukin 6 (IL-6), and the lipid markers apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)] and performed a meta-analysis of these outcomes for relevant recurrently published biomarkers. As secondary purpose, we screened for other new biomarkers that are not enlisted above, in order to reveal additional, potentially useful biomarkers.

2 | METHODS

2.1 | The systematic search

A systematic literature review was performed in PubMed and Embase, to gather all published literature published between the first of October 2009 and September 3, 2020. Details of the search terms are available in Table S1; in general, the search terms were related to adults/general population, as well as to (childhood) cancer survivors, and combined with all enlisted nine separate biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apoB, and lp(a)) and the MetS. The AMSTAR checklist for systematic reviews was followed.[52] All titles and abstracts were screened by two independent reviewers (VP and SSvS), who were blinded to each other's judgment. Studies were included if they had the MetS as outcome, and one or more newer biomarker(s) as independent variable included in the model in predictive studies, or as discriminative variable in diagnostic studies. For studies performed in CCS, no limits were set for sample size or age. General population studies were eligible if the sample size was roughly 250 or larger and if 75% or more of this population was below 65 years of age, as they have comparable levels of frailty to a young adult survivor population.[5,7,8] We excluded studies with older adults since they are expected to have higher levels of frailty, comorbidities, and aging factors, which may be confounders in the correlation between the newer biomarker and the metabolic syndrome. Multivariable analysis was mandatory for article inclusion of studies that investigated the prediction of MetS.

Studies were excluded if all included patients had an elevated biomarker; if all or none of the subjects had the MetS; if it was a selected cohort with pre-existing comorbidities (i.e., familial hypercholesterolemia, psoriasis, schizophrenia, polycystic ovary syndrome, obesity, and hypertension); if all patients suffered from MetS endpoint(s) such as T2DM, cardiovascular or cerebrovascular disease, or non-alcoholic fatty liver disease; if the article was a review, case study, expert opinion, or conference abstract; if the article was written in a language other than English or Dutch; or if the full text was unavailable (see Appendix S1 for an overview of selection criteria). Studies were only

included if the outcome was presence or absence of MetS; those with separate MetS components or MetS risk score as outcome were out of the scope of this review. After all articles were screened based on title and abstract, the judgments were unblinded. Discrepancies were discussed and resolved by the two reviewers (VP and SSvS), and where necessary, two senior experts were consulted (MMvdHE and SJCMMN). A cross-reference check was performed with Scopus, to screen all forward and backward citations of included studies. The articles found by the cross-reference check were screened likewise. A flow diagram with the number of included and excluded articles and reasons for exclusion illustrates this process (Figure 1).

2.2 | Risk of bias assessment

The QUIPS tool was applied for critical appraisal of predictor studies[53,54] (Table S2) and QUADAS-2 tool for diagnostic studies (Table S3). Definitions for low risk of bias judgment are shown in Appendix S1. In case of doubt, the study was discussed with both reviewers and senior experts (VP, SSvS, MMvdHE, and SJCMMN).

2.3 | Data extraction enlisted novel biomarkers

Data of all included articles were extracted and summarized; the summaries of the enlisted newer biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apoB, and lp(a)) are depicted in Table S4A–V. Data of interest are details regarding the size of the population and its type (survivors and their previous diagnosis or general population), the study design (cross-sectional or longitudinal and retrospective or prospective), the biomarker (which and how it was measured), the exact outcome (MetS definition), and statistical analysis of choice. For studies investigating the diagnostic value of the biomarker for MetS, outcomes of interest were area under the curve (AUC) of receiver operating characteristic (ROC) curves, sensitivity, and specificity. For the studies evaluating the predictive value of the biomarker of later development of the MetS, odds ratios (ORs) or beta-coefficients of multivariable logistic regression models, or hazard ratios (HRs) from multivariable Cox Proportional Hazards analysis were extracted from the publications.

2.4 | Summary of evidence

The Grading of Recommendations Assessment Development and Evaluation (GRADE) tool was applied to summarize the quality of the evidence for each biomarker, per clinical research question (diagnosing or predicting MetS) and per population (general population and CCS).[55] The level of evidence was classified as insufficient, very low, low, moderate, and high (Table S4).[55] The applied thresholds for biomarkers are shown in Table S5. An overview was made for studies assessing the same independent variables and outcome (Table S6).

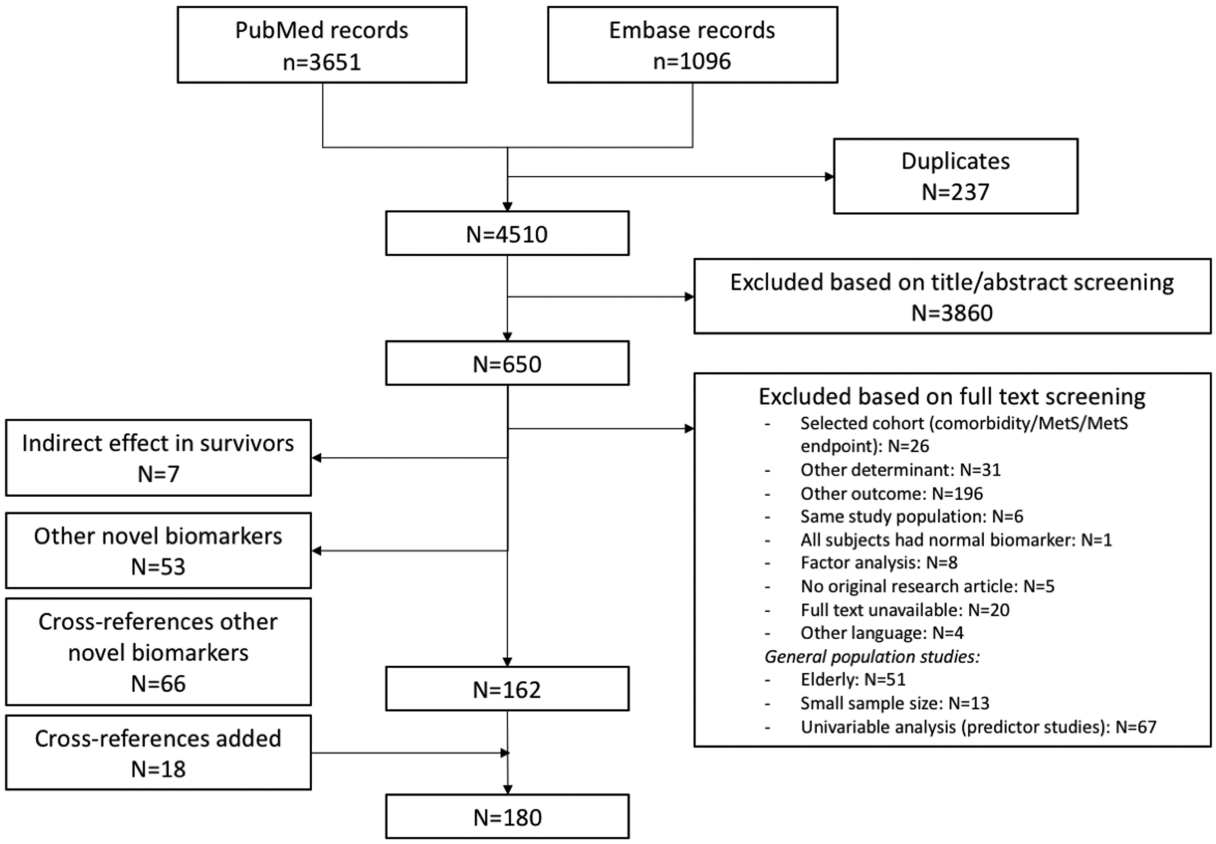

FIGURE 1 Flow chart of included and excluded articles from the systematic literature search

2.5 | Data extraction non-enlisted biomarkers

As secondary objective, we screened all articles for other biomarkers than the above enlisted nine biomarkers of our main interest (non-enlisted biomarkers). Details are discussed in Part 2 of Appendix S1. These non-enlisted biomarkers were evaluated for presence of an effect if there were four or more publications with this biomarker in our search. As we did not search for these biomarkers systematically, evidence quality was not assessed with GRADE.

2.6 | Meta-analysis

A meta-analysis was performed of relevant enlisted biomarkers with at least three publications on the same outcome measures and, if applicable, adjusted for the same covariates. Dichotomous outcomes were considered as comparable if the applied threshold differed less than the intra- and inter-assay variability for the biomarker as reported in literature. A random effects model with inverse variance weighting was used to estimate a pooled overall outcome measure. Overall heterogeneity (I-squared) and between-study variance (tau-squared) were calculated.[56] Meta-analysis was performed with the package *meta* in R.[57]

3 | RESULTS

3.1 | Study selection

As shown in the flow chart (Figure 1), the literature search in PubMed and Embase yielded a total of 4,510 unique records. After title and abstract screening, 650 full-text articles were reviewed, after which 162 relevant studies remained. Backward and forward citation searching identified 18 additional studies. Hence, a total of 180 studies were identified that reported on the diagnostic and/or predictive value of one or more of the enlisted nine biomarkers of interest. Only five studies among the 180 were performed among a population of CCS.[58–62] All other studies were performed in the general population.

Among 180 studies which included data regarding the 9 enlisted biomarkers, 60 also reported the value of other, non-enlisted newer biomarkers. Furthermore, we identified 119 other studies that only investigated non-enlisted newer biomarkers (other than the nine of our main interest), yielding a total of 179 studies for our secondary objective.

A detailed description of the critical appraisal of each of the 180 included studies for the nine predefined biomarkers is provided in the supporting information (Tables S2 and S3).

3.2 | Used metabolic syndrome definitions

In the included studies, a variety of MetS definitions was used of which the most common are described in Table 1, and the applied definition per study is depicted in Table S4. The applied biomarker thresholds are summarized in Table S5.

3.3 | Evidence for newer, enlisted biomarkers as (additional) diagnostic criterion for metabolic syndrome

Twenty-nine studies reported on the diagnostic value of one or more of the nine enlisted newer biomarkers. These were all performed in the general population without a history of cancer. Six studies had a Caucasian study population.[63–68] The number of studies per biomarker ranged between 0 [IL-1 and lp(a)] and 12 (adiponectin). The biomarker studied in the largest total number of participants was uric acid (73,190 participants). The relevant data extracted from each study, as well as the summary of evidence scored with the GRADE tool for each biomarker, are provided in the supporting information (Table S4). For each biomarker, a description of the number of studies and participants and a summary of the several diagnostic outcomes are provided in Table 2.

Whereas, ideally, the additional diagnostic value of a biomarker would be tested by comparing the AUC, sensitivity and specificity for a model containing only relevant covariates, versus a model containing covariates and the newer biomarker, this method was used in only two of the 29 studies.[65,81] One study compared the AUC of the biomarker with the AUC of waist circumference.[81] Most studies, however, only reported the AUC of the biomarker, either unadjusted or adjusted for age, sex, and sometimes BMI or waist circumference. Therefore, interpretation of the additional value is limited by detection and confounding bias for most of the biomarkers.

The overall summary of our findings, with a conclusion about the diagnostic value of each biomarker in the general population and in survivors based on the GRADE assessment, is shown in Figure 2. Of the nine investigated biomarkers, four were identified as valuable diagnostic biomarkers for MetS: leptin (high quality of evidence), uric acid (moderate quality), adiponectin, and hsCRP (both low quality). In addition, apoB may be valuable, although based on only one study with moderate quality of evidence. TNF-alpha and IL-6 appeared to be unusable, based on one low-quality study testing both biomarkers. For IL-1 and lp(a), no studies were found.

3.4 | Evidence for newer, enlisted biomarkers as independent predictor of metabolic syndrome

In total, 162 general population studies, and 5 survivor studies (two in acute lymphoblastic leukemia [ALL] survivors, two in survivors of hematological malignancies, and one in survivors of heterogeneous tumors),[58–62] investigated the role of one or more of the nine enlisted, newer biomarkers as independent predictors of MetS. Twenty-six of the general population studies had a Western/Caucasian study population.[65,67,68,87,93–100,166–171,197–199,218–220,231,233] The number of general population studies per biomarker ranged between

TABLE 1 Commonly used metabolic syndrome definitions in selected studies

	NCEP ATP III	IDF 2006	Joint interim statement/harmonized definition	Japanese Obesity Society	Chinese diabetes society	Children and adolescents	Modified with BMI instead of waist circumference
Required for MetS diagnosis	3 or more criteria	Obesity plus 2 or more criteria	3 or more criteria	Obesity plus 2 or more criteria	3 or more criteria	3 or more criteria	
Obesity	Waist circumference >102 cm (men) or >88 cm (women)	Waist circumference >90 cm (men) or >80 cm (women)	Waist circumference with ethnic-specific thresholds	Waist circumference >85 cm (men) or >90 cm (women)	Body mass index ≥25 kg/m^2	Waist circumference ≥90th percentile	Body mass index ≥30 (Caucasians) or ≥25 (Asians) kg/m^2
Insulin resistance	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥6.1 mmol/L or treatment	Fasting plasma glucose ≥6.1 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	
Dyslipidemia	Triglycerides ≥1.7 mmol/L or treatment	Triglycerides ≥1.7 mmol/L or treatment	Triglycerides ≥1.7 mmol/L or treatment	Triglycerides ≥1.7 mmol/L, or HDL cholesterol <1 mmol/L (men) or <1.3 mmol/L (women), or treatment	Triglycerides ≥1.7 mmol/L, or HDL cholesterol <0.9 mmol/L (men) or <1.0 mmol/L (women), or treatment	Triglycerides ≥1.7 mmol/L or treatment	
	HDL cholesterol <1 mmol/L (men) or <1.3 mmol/L (women) or treatment	HDL cholesterol <1 mmol/L (men) or <1.3 mmol/L (women) or treatment	HDL cholesterol <1 mmol/L (men) or <1.3 mmol/L (women) or treatment			HDL cholesterol <1 mmol/L or treatment	
Hypertension	≥130/85 mmHg or treatment	≥130/85 mmHg or treatment	≥130/85 mmHg or treatment	≥130/85 mmHg or treatment	≥140/90 mmHg or treatment	≥130/85 mmHg or treatment	

TABLE 2 Summary of outcomes

Biomarker	Total number of studies and participants	Outcome	Number of studies	Range
Summary of outcomes in diagnostic studies				
Leptin, in general population	6 studies, 8,209 participants[68–73]	AUC	5[68–70,72,73]	0.68–0.93
		Sensitivity	3[69,71,73]	48.0–92.6%
		Specificity	3[69,71,73]	56.3–72.0%
Uric acid, in general population	9 studies, 73,190 participants[66,73–80]	AUC	7[66,73–75,77,78,80]	0.56–0.85
		Sensitivity	3[73,76,77]	38.0–76.0%
		Specificity	3[73,76,77]	56.0–85.0%
Adiponectin, in general population	12 studies, 21,888 participants[63,65,67–70,81–86]	AUC	12[63,65,67–70,81–86]	0.55–0.92
		Sensitivity	2[69,84]	64.7–69.3%
		Specificity	2[69,84]	56.0–66.0%
hsCRP, in general population	7 studies, 18,211 participants[64,74,87–91]	AUC	6[64,74,87–89,91]	0.55–0.74
		Sensitivity	3[89–91]	51.0–69.0%
		Specificity	3[89–91]	56.6–72.0%
ApoB, in general population	1 study, 8,120 participants[92]	AUC	1[92]	0.68
TNF-alpha, in general population	1 study, 976 participants[64]	AUC	1[64]	0.54
IL-6, in general population	1 study, 976 participants[64]	AUC	1[64]	0.56
IL-1 and lp(a), in general population	No studies	n.a.	n.a.	n.a.
All biomarkers, in survivors	No studies	n.a.	n.a.	n.a.
Summary of outcomes in prognostic studies				
Uric acid, in general population	78 studies, 447,559 participants[74–77,79,80,93–164]	OR dichotomous	21[75,96,97,101–105,109,115,118,119,125,127,128,135,141,148,157,158,165]	1.00–5.17
		OR per unit	19[74,76,99,100,105,106,110,111,116,121,123,124,126,144,146,149,150,159]	1.001–2.14
		OR per unit log-transformed	2[77,163]	1.16, 2.08
		OR highest quantile	24[94,103,112,114,117–120,122,129,132,133,136,138–140,142,143,151–153,157,162,164]	1.00–8.04
		HR dichotomous	5[77,80,107,131,161]	1.06–2.99
		HR per unit	4[79,146,147,155]	1.10–2.35
		HR per SD	3[107,108,156]	0.86–1.36
		HR highest quantile	8[79,107,113,130,147,154–156]	0.74–3.47
		HR per unit longitudinal increase	2[107,146]	1.05, 1.31
		RR per unit log-transformed	1[137]	7.25 for men, 13.26 for women
		RR per SD	1[93]	1.10
		RR per 1.4 mg/dl	1[98]	1.54 for men, 1.82 for women
		RR highest quantile	2[93,160]	1.69, 1.76
		PR	2[95,145]	1.47, 2.10
		IRR	1[95]	1.73

TABLE 2 (Continued)

Biomarker	Total number of studies and participants	Outcome	Number of studies	Range
Uric acid, in survivors	2 studies, 390 survivors[58,59]	MetS prevalence in uric acid Q4 vs. Q1–3	1[59]	28.5% vs. 12.5% ($p = 0.0044$)
		MetS component(s) prevalence high vs. low uric acid	1[58]	60% vs. 24% ($p = 0.04$)
Adiponectin, in general population	38 studies, 56,656 participants[65,67,69,81–83,86,166–196]	OR dichotomous (low adiponectin)	2[170,172]	0.90, 2.68
		OR per unit	9[67,167,169,174,176,180,181,186,191]	0.66–1.08
		OR per 5 units	1[81]	0.82 for men, 0.90 for women
		OR per unit log-transformed	4[86,168,178,183]	0.10–0.67
		OR per SD	2[192,194]	0.50–0.91
		OR per unit log-transformed Z-score	1[69]	0.76 for boys, 0.69 for girls
		OR highest quantile	13[81–83,173,175,177,179,182,185,192,194–196]	0.10–0.67
		OR lowest quantile	6[65,171,184,189,190,193]	1.82–18.6
		HR high baseline and increase during follow-up vs. low baseline and decrease	1[188]	0.33
		HR decreased at follow-up	1[171]	4.37
		Time ratio of developing MetS Q1 vs. Q4	1[187]	0.15 (=85% shorter time to develop MetS)
		Baseline ratio (value in MetS subjects divided by value in non-MetS, adjusted for covariates)	1[166]	1.27
Adiponectin, in survivors	3 studies, 139 survivors[58,60,62]	OR highest quantile at baseline and follow-up	1[62]	0.5 (n.s.) for baseline, 0.9 (n.s.) for follow-up
		HR dichotomous (low adiponectin)	1[58]	6.7
		P value of Kruskal-Wallis test median adiponectin in 0, 1, 2–4 MetS components	1[60]	n.s.
hsCRP, in general population	32 studies, 119,138 participants[87,89,90,98,99,110,126,130,166,168,179,197–217]	OR dichotomous	2[200,203]	1.20, 2.74
		OR per unit	7[87,99,110,205,206,215,217]	1.007–2.97
		OR per unit log-transformed	4[90,126,168,211]	1.15–3.2
		OR per SD	1[199]	1.21
		OR per SD log-transformed	2[89,212]	0.96, 1.07
		OR highest quantile	11[179,198,201,204,208–210,212–214,216]	1.07–7.11
		OR highest of three groups (<1.0, 1.0–3.0 and >3 μg/ml)	3[202,207,211]	1.65–18.86
		HR per unit log-transformed	1[130]	1.15
		RR per threefold increase	1[98]	1.13
		Baseline ratio	1[166]	0.80 (n.s.)
		P value of likelihood test in multivariable model	1[197]	n.s.
hsCRP, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	7.26
ApoB, in general population	10 studies, 66,924 participants[97,168,218–225]	OR dichotomous	1[97]	2.55
		OR per unit	1[168]	2.99
		OR per 30 mg/dl	1[220]	1.76 for men, 2.10 for women
		OR per SD	1[223]	1.56
		OR highest quantile	6[218,221–225]	0.96–6.03

(Continues)

TABLE 2 (Continued)

Biomarker	Total number of studies and participants	Outcome	Number of studies	Range
		OR highest of three groups (<90, 90–119 and ≥120 mg/dl)	1[219]	2.69 for men, 1.69 for women
		RR per SD	1[223]	1.17 (n.s.)
		RR highest quantile	1[223]	1.79
ApoB, in survivors	No studies	n.a.	n.a.	n.a.
Leptin, in general population	17 studies, 28,797 participants[68,69,72,167,168,172,179,180,183,191,192,196,226–230]	OR dichotomous	1[172]	2.39
		OR per unit	4[167,180,191,229]	0.96–1.91
		OR per 10 ng/ml	1[226]	1.06 (adjusted for WC), 1.22 (adjusted for BMI)
		OR per unit log-transformed	2[168,183]	1.47, 2.76
		OR per SD	3[68,192,228]	1.01–1.31
		OR per unit log-transformed Z-score	1[69]	1.81 for boys, 1.32 for girls
		OR highest quantile	6[72,179,192,196,227,230]	1.16–3.02
Leptin, in survivors	3 studies, 139 survivors[58,60,62]	OR highest quantile at baseline and follow-up	1[62]	4.8 for baseline, 5.7 for follow-up
		MetS component(s) prevalence high vs. low leptin	1[58]	54% vs. 17% ($p = 0.03$)
		P value of Kruskal-Wallis test median adiponectin in 0, 1, 2–4 MetS components	1[60]	n.s.
IL-6, in general population	5 studies, 3,370 participants[67,83,206,231,232]	OR per unit	2[67,206]	0.98–1.47
		OR highest quantile	2[83,232]	0.98 (n.s.), 4.10
		P value in multivariable model	1[231]	n.s.
IL-6, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	1.53 (n.s.)
Lp(a), in general population	5 studies, 15,162 participants[207,233–236]	OR dichotomous	1[207]	8.27
		OR highest of three groups (<18.40, 18.40–33.84 and ≥33.85 μg/ml)	1[234]	0.82 (n.s.)
		OR per unit	1[235]	1.0 (n.s.)
		OR highest quantile	1[236]	0.45
		HR highest quantile	1[233]	1.01 (n.s.)
Lp(a), in survivors	No studies	n.a.	n.a.	n.a.
IL-1, in general population	4 studies, 1,594 participants[166,206,232,237]	OR per unit	2[206,237]	2.28 (IL-1alpha), 1.009, 2.01 (IL-1beta)
		OR highest quartile	1[232]	0.98 (n.s.)
		Baseline ratio	1[166]	1.17 (suggests effect in other direction)
TNF-alpha, in general population	3 studies, 1,458 participants[206,231,232]	OR per unit	1[206]	1.45
		OR highest quartile	1[232]	0.78 (n.s.)
		P value in multivariable model	1[231]	n.s.
TNF-alpha, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	0.52 (n.s.)

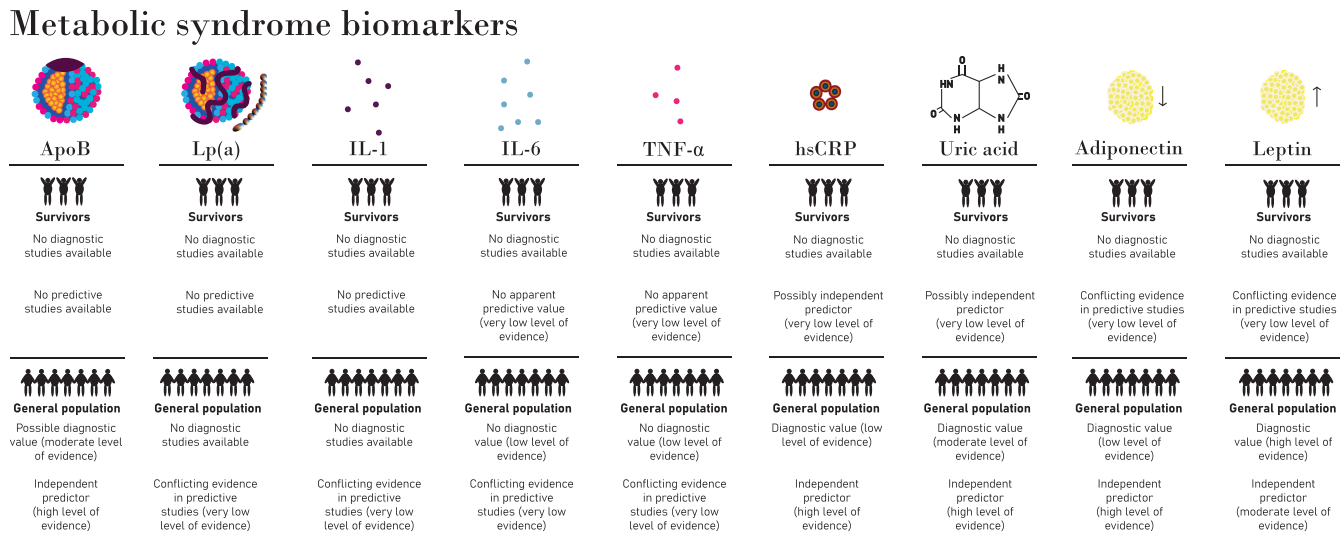

FIGURE 2 Summary of conclusions: predictive and diagnostic value of novel biomarkers for the MetS

3 (TNF-alpha, 1,458 participants in total) and 78 (uric acid, 447,559 participants in total). Two of the survivors studies had a Western/Caucasian study population[58,59]; the others were performed in Japan,[60] Malaysia,[61] and Mexico.[62] The number of survivors studies per biomarker ranged between zero [IL-1, apoB, and lp(a)] and three (adiponectin and leptin). The biomarker studied in the largest total number of survivors was uric acid (390 survivors). The relevant data extracted from each study, as well as the summary of evidence scored with the GRADE tool for each biomarker, are provided in the supporting information (Table S4). For each biomarker, a description of the number of studies and participants and a summary of the several prognostic outcomes are provided in Table 2.

A common analysis strategy in these studies was to divide the biomarker value in quantiles, with thresholds that may differ per study. Not all participants in the highest or lowest quantile always had a biomarker value that would be classified as abnormal according to reference values. This may attenuate its value in predicting MetS. On the other hand, this bias towards the null hypothesis increases the effect of true positive findings. Also, several studies tested a dose–response effect by comparing the effect on MetS across the quantiles. Studies can be compared on whether a dose–response effect was observed or not.

Figure 2 shows the overall summary of our findings, consisting of a conclusion about the role of each biomarker as independent predictor of MetS in the general population and in survivors, after GRADE assessment. Five biomarkers were identified as independent predictors of MetS in the general population: uric acid, adiponectin, hsCRP, apoB (all high quality of evidence), and leptin (moderate quality). There is conflicting evidence for the value of TNF-alpha, IL-1, IL-6, and lp(a) (very low quality of evidence). Among survivors, uric acid and hsCRP may be valuable as prognostic biomarkers, based on two and one studies, respectively, with very low quality of evidence. There is conflicting evidence for the prognostic value of adiponectin and leptin (very low quality). TNF-alpha and IL-6 appear not to be independent predictors, based on one very low quality study testing both biomarkers. For IL-1, apoB, and lp(a), no studies were found.

3.5 | Meta-analysis of most relevant findings of enlisted biomarkers

We aimed to perform a meta-analysis of the most promising biomarkers: uric acid, adiponectin, leptin, hsCRP, and apoB. For diagnostic studies, only the AUC is suitable for meta-analysis, due to different thresholds used for sensitivity and specificity (Table S6). For predictor studies, only dichotomous and continuous (per unit or per unit log-transformed) studies are useful. Many studies use quantiles, but these are unsuited for meta-analysis: cut-offs between the quantiles depend on the range and distribution in each study population and are therefore insufficiently comparable between studies to perform a meta-analysis.

A wide variety of outcome measures was used in the studies, and many studies performed an analysis that was unsuited for meta-analysis. Also, there was variance in thresholds used for dichotomous outcomes, as well as in covariates in multivariable models. Therefore, we were unable to retain at least three sufficiently comparable studies for most biomarkers, and for most outcomes, in order to perform a meta-analysis. For a few biomarkers, enough studies were eligible for meta-analysis, because the authors also published crude outcomes, and outcomes that were only age and sex adjusted (Table S6).

We were able to perform a meta-analysis for the prognostic value of uric acid (hyperuricemia and continuous uric acid levels) and for the diagnostic value of hsCRP. We estimated the pooled OR for the association between hyperuricemia and MetS, adjusted for age and sex (four studies,[101–104] with threshold variability accepted of

10%,[238] OR 2.94, 95%CI 2.08–4.15); the pooled OR per unit increase in uric acid, unadjusted (three studies,[99,105,106] OR 1.086, 95%CI 1.066–1.106); and the pooled AUC for hsCRP, also unadjusted (three studies,[74,87,88] AUC 0.71, 95%CI 0.67–0.74).[99,106] Forest plots are shown in Figure 3. Unfortunately, many studies could not be included, and the reported estimators are not adjusted for relevant covariates, in particular age and sex for some, and overweight, insulin resistance, and smoking for all.

3.6 | Other, non-enlisted biomarkers

In Table S7, 179 articles for all other biomarkers for diagnosis or prognosis of MetS are enlisted, and the main data are summarized. These included ratios of our studied biomarkers. All studies investigating leptin/adiponectin ratio as prognostic[62,68,69,167,172,173,239] or diagnostic study[68–70,173,239,240] showed a possible relevance. Apolipoprotein A1 (apoA1) and apoB/apoA1 ratio seem valuable in predicting the MetS (six studies with a protective effect of apoA1[97,219–222] and eight studies with an effect of increasing risk of increasing apoB/apoA1 ratio[92,97,221,222,241–244]). There are two studies reporting a diagnostic value of apoB/apoA1 ratio.[92,221] Other recurrently reported, potentially useful biomarkers were Gamma GT, (non-high sensitivity) CRP, ferritin, leukocyte count, hemoglobin and urine pH, and sodium excretion.

4 | DISCUSSION

This is the first systematic literature review investigating newer biomarkers for metabolic syndrome (MetS) in CCS, with the aim to obtain the highest level of evidence by including validated tools for risk of

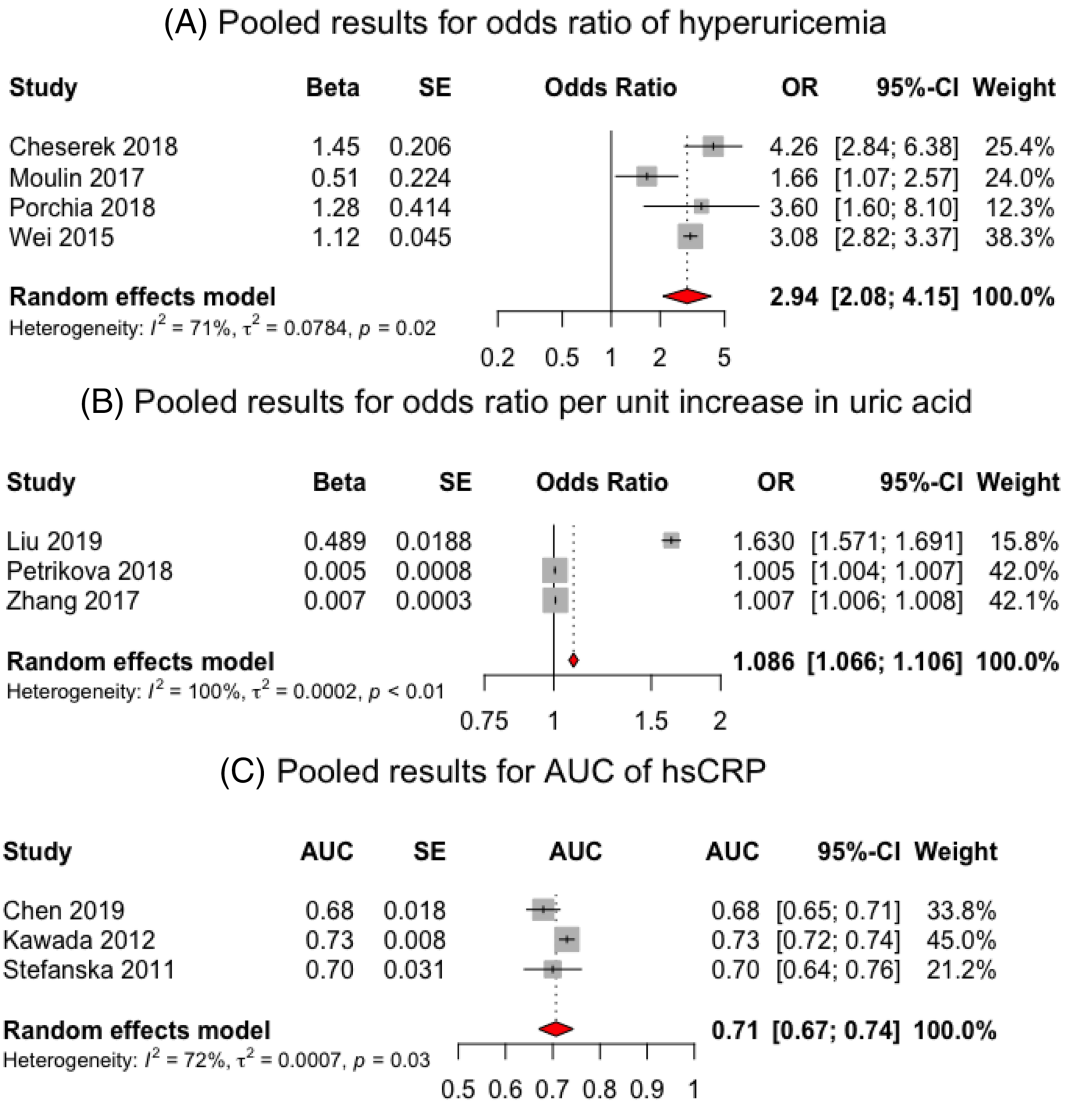

FIGURE 3 Forest plots for different study-specific outcomes. (A) Odds ratio (OR) for hyperuricemia. (B) OR for per unit increase in uric acid. (C) Area under the curve (AUC) of hsCRP. The sizes of the square boxes on the forest plots are proportional to the total number of patients in the selected trials

bias assessment and summary of evidence, and by performing a meta-analysis.

For five biomarkers, numerous studies with moderate to high quality of evidence were found for diagnosing and predicting MetS: uric acid, adiponectin, leptin, hsCRP, and apoB. The evidence was not sufficient to confirm the value of candidate biomarkers lp(a), IL-1, IL-6, and TNF-alpha.

Meta-analysis of eligible studies showed a predictive value of uric acid for MetS, with a positive association, and a diagnostic value for hsCRP.

These findings suggest that uric acid, adiponectin, leptin, hsCRP, and apoB may be used in a screening setting for CCS, in addition to standard MetS criteria, in order to provide better diagnosis and prediction of MetS (risk). Systematic reviews in other populations have identified not only elevated leptin,[245] uric acid,[245–248] and low (HWM) adiponectin,[245,249,250] but also Il-6[245] and TNF-alpha[245] as potential MetS biomarkers.

As anticipated, the number of publications for survivors on this topic was rather limited: we identified only five studies in CCS specifically, which found a possible predictive value for hsCRP and uric acid, and conflicting or no evidence for the value of adiponectin, leptin, and TNF-alpha. Disadvantages of these survivor studies were low patient numbers and moderate to high (detection and confounding) bias risk. No studies investigated the diagnostic value of newer biomarkers. Survivor studies with information on altered biomarker values but no direct comparison between biomarker and MetS occurrence were excluded.[60,251–260] We expected to miss many relevant studies when designing the study, if we based our conclusions only on survivor studies. Therefore, evidence in the younger general adult population without childhood cancer history was included in our search as well, leading to 175 general population studies with relevant data which were generalizable to young adult survivors.

CCS can have an increased risk to develop MetS, in particular after treatment with cranial and/or abdominal radiotherapy, intensive chemotherapy, nephrectomy, adrenalectomy, or stem cell transplantation.[43,261–269] These therapies can lead to several underlying conditions that can increase the risk for (components of) MetS, such as hypothalamic damage, growth hormone deficiency, pancreatic beta cell dysfunction, hypogonadism, hypothyroidism, and altered body composition with increased abdominal fat.[43,261–269]

Furthermore, it is well acknowledged that in CCS, the biological age progresses faster than their true age, as can be derived from their high level of frailty.[4–9] Previous studies have shown that the physiologic reserve of CCS with a median age of 33 is similar to that of adults in the general population who are aged 65 years.[6] For this reason, we included studies investigating biomarkers for MetS in the general population, with >75% of participants aged below 65 years, as may be very well applicable to CCS. We excluded studies investigating MetS biomarkers among elderly people on purpose, since they have an even higher level of frailty than CCS, comorbidities, and aging factors, which may be confounders in the association between the newer biomarker and metabolic syndrome. We considered that extrapolating conclusions from a general elderly population to CCS could draw invalid conclusions. Based on this approach, all available literature applicable to survivors is now discussed in this review, as it includes both survivor studies as well as all generalizable data from a reasoned selection of the general population studies.

On the other hand, several studies excluded people with certain chronic illnesses.[74,75,82,83,167,174–180,226] This may limit applicability of results to the population of CCS, in which the prevalence of comorbidities is high.[3,25,256,270] This was taken into account when scoring the risk of bias. Additionally, childhood cancer (treatment)-related long-term side effects, such as altered fat distribution, sarcopenic obesity, and hormonal disbalances, may play a survivor specific role in the pathogenesis of MetS[11]; development of future studies that apply the use of biomarkers in large cohorts of CCS is therefore important.

Due to differences in study designs and statistical analyses, a wide variety of outcome measures was used. There was also substantial diversity in follow-up time in longitudinal studies. By employing the GRADE tool for summarizing evidence, we were able to draw conclusions for each biomarker from this heterogeneity of results. The meta-analysis was based on few studies, as many studies could not be included. Also, heterogeneity was high in the meta-analysis on uric acid per unit increase, as the study of Liu et al.[105] had a remarkably higher OR than the other two studies.

Furthermore, although the ability of different MetS definitions to predict diabetes and CVD appears to be similar,[271,272] the use of different definitions (Table 1) can lead to differences in occurrence of MetS. There are subtle differences between the definitions that were mostly used in the included studies (Table 1). The potential consequence of choice of definition is illustrated by studies that tested the biomarker use in diagnosing or predicting MetS according to multiple definitions and sometimes found different results depending on the definition used.[67,71,83,200] Therefore, comparing different studies and interpreting results of the meta-analysis requires some caution, as a full comparison of the studies is often not possible.

Adiposity, and hence the MetS, can be underdiagnosed in survivors, due to altered body composition after radiotherapy, stem cell transplantation, or amputations. For clinical applicability to survivors, it is important that newer biomarkers play an independent role in MetS, and measurement of newer biomarkers is only useful when their effect is not yet captured by established MetS components. Therefore, we did not investigate routine dyslipidemia and insulin resistance markers in our search (e.g., LDL and HOMA-IR). Although apoB and lp(a) are also lipid markers, they are of interest because they are better predictors of atherogenicity than triglycerides, HDL and LDL—particularly apoB, because it gives an estimate of the total number of circulating atherogenic particles.[273–275]

In this light, it is also favorable that studies adjust for MetS components, such as adiposity and insulin resistance, in order to adjust for potentially major correlations and interactions[181,276–278] and to yield the independent/additional diagnostic and predictive value of the biomarker. Furthermore, it remains important to evaluate other traditional risk factors, including smoking, physical activity, socio-economic status, and family history[170,279] In addition, genetic profile may still be relevant for MetS risk, although so far this is not included in standard

screening.[280–282] Risk of detection and confounding bias remains high, especially in the diagnostic studies, as many studies did not adjust for MetS components and traditional risk factors. In particular for the diagnostic studies, a risk of (detection and) confounding bias remained.

The MetS is defined as a cluster of symptoms such as obesity, hypertension, impaired glucose tolerance, and dyslipidemia.[11] These clustered symptoms are related to each other: an imbalance in energy intake and consumption causes a cascade of increased (visceral) adiposity, increased circulating free fatty acids and decreased adiponectin (which causes also an increase in insulin resistance), and high levels of pro-inflammatory and pro-thrombotic mediators, such as TNF-alpha, IL-1, and IL-6.[11,34] Insulin resistance is associated with a lowered excretion of uric acid by the kidneys and higher uric acid production.[283,284] The adipokines leptin and adiponectin are produced by adipocytes.[285] Low leptin values trigger metabolic, behavioral, and endocrine responses that aim at a preservation of the fuel reserves of the body.[286] Adiponectin enhances insulin sensitization and suppresses inflammation and cell death.[286–289] Another important molecule is apoB: all atherogenic lipoproteins carry one single apoB molecule as their structural protein, and therefore, apoB represents the atherogenic burden.[290] Serum apoB is a strong predictor of cardiovascular risks[273,291,292] and comes in as an important player for the MetS in this review as well. One of the low density lipoproteins carrying an apoB molecule is Lp(a).[293] The interpretation of Lp(a) values in an individual can be difficult due to a high heterogeneity and wide distribution of Lp(a) concentrations.[294] Although evidence for relevance of Lp(a) for MetS evaluation in survivors was unavailable, it remains a marker of interest, since elevated Lp(a) levels were an independent predictor for cardiovascular and cerebrovascular outcomes[295–303] and were inversely associated with T2DM.[304]

An important inflammatory marker is (hs)CRP, which is synthesized by hepatocytes[305,306] in response to infection, inflammation, tissue damage, and malignant neoplasia.[305,306] CRP binds to LDL[305,307] and may have a causal role in atherogenesis,[305] as it is present in atherosclerotic plaques.[305,308] Inflammatory markers may reflect a transient state instead of chronic state of inflammation.[201] Still, in the study of Oda and Kawai,[309] the diagnostic value of hsCRP was reproducible when the measurement was repeated after 1 year. Many studies had a high CRP[74,166,202,203] or infection[88,204–206,232] as exclusion criterion. Regarding inflammation, smooth muscle cells, endothelial cells, and macrophages produce cytokines such as IL-1 and IL-6[310–312] in reaction to metabolic stress,[312,313] by other inflammatory mediators such as interferon-gamma and TNF, and cholesterol itself.[312] Still, the evidence for the usefulness as marker for the MetS is rather limited.

Due to the systemic nature of MetS, our secondary objective to reveal other interesting biomarkers yielded many markers. Interesting markers for further research include Gamma GT, ferritin, leukocytes, and hemoglobin. In several studies, biomarkers were related to each other, as MetS components are related as well.[314] In one study, leptin was inversely associated with uric acid excretion[314]; in another, a synergistic effect between hsCRP and high molecular weight adiponectin was found.[315] Also, ratios of biomarkers (e.g., leptin/adiponectin, apoB/apoA1) include extra information and may be better diagnostic or prognostic agents than single biomarkers. Future studies may investigate the value of combining biomarkers.

Some limitations are present in this systematic literature.

Many of the included studies had a cross-sectional design, which is suboptimal to investigate causality; this was taken into account for the GRADE and level of evidence. Some authors conducted prospective longitudinal studies[89,107,171,201] and associated MetS risk at end of follow-up with baseline and/or change in biomarker level. Study designs even more suitable for determining prediction and causality include prediction models and Mendelian randomization.[108,316–318] These study designs require more time and financial resources and large cohorts. These types of studies were either not performed or unsuitable for our research question.

Many studies were performed among Asian cohorts. Asian people are more susceptible to insulin resistance,[319,320] which is accounted for in lower waist circumference thresholds. Additionally, there may be an ethnicity specific component in the relationship between biomarker and MetS.[321–328] This may limit the applicability to a Caucasian population.

For this literature study, we focused on diagnosis and prediction of the full MetS; other outcomes such as resolution of the MetS,[329] components of the MetS, CVD, or T2DM were out of scope.[302,330–341] Therefore, our findings do not provide a complete overview of the use of the newer biomarkers in diagnosing and predicting cardiovascular risk factors in CCS.

We have two suggestions for future research that are relevant for the implementations of our findings in the follow-up of CCS. The newer biomarkers could be added as a sixth criterion for MetS. This application can be especially of value in cases of doubt of MetS diagnosis for individuals who had abdominal irradiation: it may be valuable to replace waist circumference with the adipokines leptin or adiponectin. This may identify MetS in more survivors and can potentially improve the predictive ability for T2DM and CVD.[337]

An important requirement for the applicability of these newer biomarkers in such a screening setting for MetS (risk) in CCS is the determination of a threshold. For uric acid, this is relatively well established (Table S5); for other biomarkers, this is less clear, as is illustrated by the range of applied thresholds (Table S5). This is partly because of the use of different assays and testing of subfractions of a biomarker, such as high molecular weight adiponectin. Also, a tradeoff between sensitivity and specificity may influence the determination of an optimal threshold.

In conclusion, based on this systematic literature search, we suggest to consider the additional use of uric acid, adiponectin, hsCRP, leptin, and apoB in the screening setting for metabolic syndrome in CCS. As our conclusions are largely based on general population studies, studies in CCS are needed. Furthermore, future studies may specifically test the use of newer biomarkers as additional MetS components and define optimal thresholds. The addition of one or more of these newer biomarkers as a criterion for MetS may lead to a newer and better classification and enhanced identification of risk of

developing T2DM and CVD, especially in CCS in whom components are difficult to evaluate in the currently applied definitions. Early intervention can delay or prevent complications and hence improve very long-term survival outcomes and quality of life.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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