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Blood-Based Biomarkers in High Grade Gliomas: a Systematic Review

Daniela Pierscianek[1,2] · Yahya Ahmadipour[1,2] · Marvin Darkwah Oppong[1,2] · Laurèl Rauschenbach[1,2] · Sied Kebir[2,3,4] · Martin Glas[2,3,4] · Ulrich Sure[1,2] · Ramazan Jabbarli[1,2]

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Abstract

High-grade gliomas (HGG) are the most common malignant primary brain tumor in adults. During the course of disease, several challenges occur, like measuring tumor burden, monitoring of treatment response, estimating the patient's prognosis, and distinguishing between true progression and pseudo-progression. So far, no blood-based biomarker has been established in the clinical routine to address these challenges. The aim of this systematic review was to analyze the present evidence on blood-based biomarkers for HGG. We systematically searched in PubMed, Web of Sciences, Scopus, and Cochrane Library databases for publications before 30th of March 2018 reporting on associations of blood-based biomarkers in HGG patients with different endpoints as overall survival, progression-free survival, and postoperative monitoring. Quality assessment of the studies according to QUIPS and STARD guidelines was performed. In accordance with the GRADE guidelines, level of evidence (I–IV) for each of the tested biomarkers was assessed. One thousand six hundred eighty unique records were identified. Of these, 170 original articles were included to this review. Four hundred fifteen different blood-based biomarkers analyzed in 15.041 patients with HGG as also their corresponding recurrent tumors. Ten predictive biomarkers reached level II of evidence. No biomarker achieved level I of evidence. In this review, 10 blood-based biomarkers were selected as most promising biomarkers for HGG: α2-Heremans-Schmid glycoprotein (AHSG), albumin, glucose, insulin-like growth factor- binding protein 2 (IGFBP-2), macrophage inflammatory protein 1δ (MIP-1 δ), macrophage inflammatory protein 3ß (MIP-3ß), neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), soluble glycoprotein 130 (Sgp130), and chitinase-3-like protein 1 (YKL-40). To further assess the clinical significance of these biomarkers, the evaluation in a larger cohort of HGG and their corresponding subgroups would be necessary.

Keywords High-grade glioma · Blood biomarkers · Systematic review

Introduction

High-grade gliomas (HGG) are the most common malignant primary brain tumors in adults with an annual incidence of approximately 3.71 per 100.000 individuals in the USA [1]. Despite multimodal treatment comprising surgery, chemotherapy and radiotherapy, the median overall survival remains poor with 16–20 months [2–4]. So far, diagnosis of HGG und monitoring of applied therapies rely upon invasive procedures like biopsy or open surgery as also on technically extensive and costly imaging techniques. Therefore, there is a need for a quick and safe tool that facilitates the estimation of patients' prognosis preoperatively, assesses the treatment response, and permits the distinction between true tumor progression and pseudo-progression. Reliable blood-based biomarkers have not been identified in the treatment of HGG in clinical routine. This is in contrast to other tumor entities (e.g., prostate cancer, hepatocellular carcinoma, malignant melanoma) where blood-based biomarkers are well established and routinely used in the clinical practice [5–7].

This review focuses on blood-based biomarkers as they can be measured non-invasively and their analysis is broadly accessible. The ideal blood-based biomarker could be used for diagnosis of HGG and the differentiation from other tumor

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✉ Daniela Pierscianek
daniela.pierscianek@uk-essen.de

[1] Department of Neurosurgery, University Hospital of Essen, 45147 Essen, Germany

[2] German Cancer Consortium, Partner Site University Hospital Essen, Essen, Germany

[3] Division of Clinical Neurooncology, Department of Neurology, University Hospital of Essen, Essen, Germany

[4] DKFZ-Division Translational Neurooncology at the West German Cancer Center (WTZ), University Duisburg-Essen, University Hospital Essen, Essen, Germany

entities, for risk stratification, for monitoring the course of disease longitudinally, and the specific treatment response [8].

In this review, we addressed publications dealing with HGG and analyzing blood-based biomarkers and their association with the diagnosis of HGG, overall survival (OS), progression-free survival (PFS), and longitudinal disease monitoring. In this context, we aimed at systemizing all currently tested blood-based biomarkers for HGG into a unique database. In addition, we report on the present level of evidence with consecutive selection of the most promising candidate biomarkers for future validation.

Material and Methods

Search Strategy and Selection Criteria

This systematic review has been established according to the PRSIMA guidelines [9]. In PubMed, Scopus, Cochrane Database, and Web of Science, we systematically searched for articles published in English before 30th of March 2018 reporting data on biomarkers in HGG, with special emphasis on glioblastoma multiforme (GBM). A complete list of search items is shown in the supplementary materials (Table S1). The search results were filed in a custom electronic database (Microsoft Access 2013; Microsoft Cooperation, Redmond, WA, USA). Duplicate entries were automatically excluded, and afterwards, DP and RJ independently screened the titles and abstracts of all collected publications. Disagreements were resolved by consensus-based discussion. DP and RJ searched the reference list of relevant publications for additional articles.

Data were taken from cross-sectional and longitudinal studies comprising patients with primary, recurrent, and secondary GBM, as well as mixed cohorts containing WHO grade III and IV patients. Studies were taken into account, if they reported on the possible associations between blood-based biomarkers and at least one of the following study goals:

- Main review endpoints defined as OS and PFS;
- Differential expression of blood biomarkers in HGG versus healthy controls and/or other tumor entities (such as low grade gliomas or non-glial tumors);
- Radiographic tumor characteristics (size, volume, contrast enhancement, tumor necrosis);
- Tumor progression and pseudo-progression;
- Changes of biomarker values after tumor surgery and/or under adjuvant treatment

The detected biomarkers must be measured in blood (serum and plasma) and be eligible for longitudinal measurements. Studies on genetic and radiographic biomarkers, as also studies evaluating biomarkers from tumor tissue and cerebrospinal fluid and studies analyzing drug level monitoring for applied chemotherapeutic agents were not included in this review.

Data Analysis

Data Collection

The analysis of all full-text manuscripts which were included to the systematic review was performed by DP and quality controlled by RJ. The following data were extracted from each publication:

- Study and populations characteristics: study design, geographic origin, study years, number of participants, baseline demographic/ clinical parameters of cohorts, applied treatment modalities, characteristics of control cohorts, and analyzed study endpoints;
- Biomarker related data: the list of tested biomarkers, frequency of sampling, and used diagnostic method;
- Study results: associations between blood-based biomarkers and the abovementioned review endpoints and quality of statistical evaluation (adjusted or unadjusted for potential confounders).

Quality Assessment

An adapted quality assessment form was generated based on the QUIPS (Quality Assessment in Prognostic Studies) tool [10] and the STARD (Standards for Reporting Diagnostic Accuracy) criteria [11] (see Table 1). The quality assessment form consisted of 11 items, which addressed the main sources of bias. For each item, the publications were allocated a score ranging from 0 to a maximum of 4 (Quality Assessment Score [QAS], 0–44 points). DP and RJ independently calculated appropriate scores for each included study. Accordingly, QAS values were integrated into the rating of the evidence level for blood-based biomarkers. Depending on the summary score, the publications were considered as high or low quality studies. The cutoff was set at presence of high risk of bias in > 2 of 11 items (OR high risk of bias in > 1 item plus low risk of bias in > 2 items), resulting in decrease of the summary score in > 8 points. Therefore, the studies scoring < 36 points were considered as low quality studies.

Classification of Blood-Based Biomarkers

Collected biomarkers were registered into a unique database (see Table S2 in the supplementary materials) containing the information on source studies, total number of patients (HGG, and, if applicable, of control groups), and results of associations for each study endpoint. The biomarker was considered eligible for postoperative monitoring, if (a) at least two postoperative samplings were performed, and (b) an association between the

Table 1 Quality assessment score for the included studies

Parameter	Description	Value
Minimizing selection bias		
Study design	Unclear	0
	Retrospective study	2
	Prospective study	4
Final cohort population	Non-representative or unclear	0
	Representative	4
Minimizing information bias		
Cohort size	1–19 patients	0
	20–100 patients	2
	> 100 patients	4
Study period/years reported	No	0
	Yes	4
Data on adjuvant treatment regime	Unclear or not reported	0
	Reported	4
Data on values or cutoffs of tested biomarkers	No values/cutoffs	0
	Incomplete data on values/cutoffs	2
	Complete data on values/cutoffs	4
Data on major GBM endpoints (OS and PFS)	Unclear or not reported	0
	Reported	4
Follow-up time reported	No	0
	Yes	4
Timing of biomarker sampling	Unclear or not reported	0
	Non-unique time-points of biomarker sampling	2
	Unique time-points of biomarker sampling	4
Repeated sampling	No or unknown	0
	Yes (at least 2 measurements for every patient)	4
Data analysis and presentation	Unclear or no adjustment for potential confounders	0
	Associations between biomarker and study endpoint controlled for major confounders	4

biomarker changes with treatment response and/or disease progression (as defined by the authors) was shown.

The Level of Evidence and Recommendations for Blood-Based Biomarkers

The level of evidence for all biomarkers was allocated to the following 4 classes according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines: high, moderate, low, and very low evidence (classes I, II, III, and IV respectively) [10]. Criteria for classification were adjusted according to the scope of the review (Table 2). According to one previous report [12], the recommendations regarding the diagnostic value of biomarkers were classified into predictive biomarkers, non-predictive biomarkers (both for biomarkers with the level of evidence class I or II), and non-conclusive biomarkers (level of evidence classes III or IV). All biomarkers identified were assigned independently by DP and RJ to a certain evidence and recommendation level.

Statistical Analysis

Study and population characteristics were analyzed using PRISM software (version 5.0, Graph Pad Software Inc., San Diego, CA, USA). Differences between continuous variables were analyzed using the Student *t* test for normally distributed and the Mann–Whitney U test for non-normally distributed data. Variables were expressed as mean standard deviation and median values or in absolute numbers and percentages, as appropriate. Differences with a *P* value of 0.05 or less were considered as statistically significant.

Results

Characteristics of Publications

A total of 1680 non-duplicating records were screened for eligibility after systematic search in the indicated databases and reference list check of relevant publications. One hundred

Table 2 Estimation of the Level of Evidence for laboratory biomarkers

Class	Definition
I	High quality
	1. Data from at least 2 cohorts with ≥ 100 patients (per study) AND
	2. Independent association between biomarker and endpoint AND
	3. Associations with both main endpoints (PFS and OS) AND
	4. Independently from applied adjuvant treatment regime AND
	5. Non-conflicting results from high quality studies
II	Moderate quality
	1. Data based on at least 100 patients (in sum) reported from high quality studies AND
	2. Independent association between biomarker and PFS or OS AND
	3. Non-conflicting results from high quality studies
III	Low quality
	Summary data from:
	1. ≥ 200 patients regardless the study quality OR
	2. ≥ 50 patients from high quality studies
IV	Very low quality
	Any lower evidence for analyzed biomarker

seventy original papers published between 1985 and 2018 were included to the final analysis (see Fig. 1 for the flow chart, as well as Table S3 in the supplementary materials for detailed characteristics of the included publications).

Considering overlapping cohorts, 415 blood-based biomarkers were evaluated in 161 different HGG populations with a total of 15.041 patients. The mean number of patients in each study was 88.48 patients (range 5–685 patients).

Fifty populations (29%) were based on US cohorts, followed by Germany ($n = 17$, 10%), China ($n = 15$; 9%), and Japan ($n = 8$; 5%). Four studies had a multicentric study design and were conducted in Europe and/or the USA.

Concerning the quality of the studies, the mean QAS value was 27.42 points (range 8–44 points). Thirty-three of 170 original articles scored > 34 points and thereby fulfilled the criteria for high quality.

Blood-Based Biomarkers for HGG

The biomarkers were integrated into a unique electronic database. The mean total number of analyzed patients for every single biomarker was 112.84 (range 6–2222). In the majority of cases ($n = 297$), the total patient load per biomarker was < 100 individuals. Mostly ($n = 268$), there was one study per biomarker. Seven biomarkers (basic fibroblast growth factor [bFGF], glial fibrillary acidic protein [GFAP], interleukin-6 [Il-6], interleukin-8 [Il-8]; tumor necrosis factor alpha [TNF-α], vascular endothelial growth factor [VEGF], CD4 cell count) were tested in 10 and more studies. More detailed information on all 415 biomarkers is shown in the supplementary materials (Table S2).

Prognostic Biomarkers in HGG Patients

We identified 79 blood-based biomarkers that showed association with OS. For 34 biomarkers, an association with OS was found in one single study. For 24 of these blood-based biomarkers, at least one study could not confirm an association with OS.

The following 14 biomarkers showed non-conflicting positive results based on high quality studies with more than 100 cumulative patients: α2-Heremans-Schmid glycoprotein (AHSG), albumin, glucose, immunoglobulin E (IgE), insulin-like growth factor binding protein-2 (IGFBP-2), insulin-like growth factor-binding protein 6 (IGFBP-6), interleukin-1 R4 (Il-1 R4), macrophage inflammatory protein 1δ (MIP-1δ), macrophage inflammatory protein 3β (MIP-3β), neutrophil–lymphocyte ratio (NLR), red blood cell distribution width (RDW), soluble glycoprotein 130 (SGP130), tissue inhibitor of metalloproteinases-1 (TIMP-1), and chitinase-3-like protein 1 (YKL-40).

For PFS, 31 biomarkers showed an association in at least one study. For 12 biomarkers, the relation to PFS was based upon a single study. For 16 biomarkers, there were conflicting results in different studies. Six biomarkers demonstrated an association with PFS in at least two independent studies. Here, albumin and IGFBP-2 were the only predictive biomarkers based on high quality studies with more than 100 patients (in sum).

Biomarkers Eligible for Postoperative Tumor Monitoring

Forty-eight blood parameters were tested in longitudinal studies utilizing multiple blood measurements. Twenty biomarkers were found to be eligible for postoperative monitoring in at least one study. Two biomarkers (IGFBP-2 and YKL-40) showed non-conflicting results in high quality studies.

Biomarkers with a Relation to MRI Data

Fourteen biomarkers showed a relation with the MRI appearance of the tumor, such as size, necrosis, contrast enhancement, or vascularization. Of them, only GFAP was tested in a large patient sample (7 studies) with non-conflicting results from high quality studies.

Biomarkers for Differentiation between True- and Pseudo-progression

Only four biomarkers (total lymphocytes count [TLC], myeloid-derived suppressor cells [MDSC], microvesicles, and circulating tumor cells [CTC]) were tested as potential biomarkers for distinction between true- and pseudo-progression. However, due to a limited number of studies (1–2

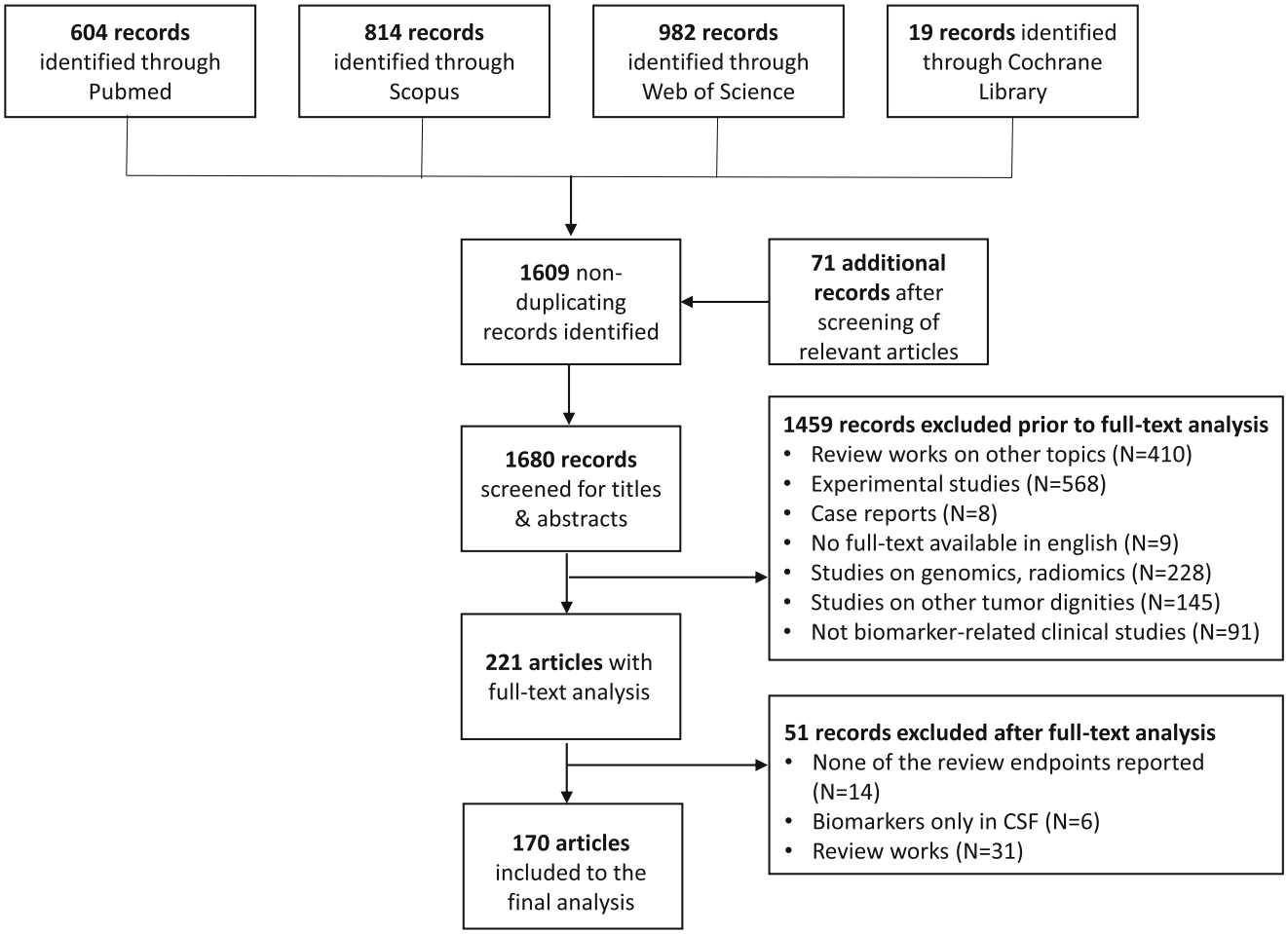

Fig. 1 Flow diagram showing selection of eligible studies

studies/biomarker) with mostly low quality (only one high quality study [13]), as well as small sample sizes (5–30 patients/study), none of the tested blood biomarkers can be currently considered for use in clinical routine.

Results of associations between the blood biomarkers and remaining review endpoints are presented in the Supplementary Materials (Tables S4–S6).

Evidence Level and Selection of Promising Biomarkers

In summary, most studies lack a sufficient level of evidence for the beneficial use of blood-based biomarkers. Of 415 biomarkers evaluated, no biomarker reached the evidence level I. However, 10 biomarkers were identified to be predictive with the evidence level II: AHSG, albumin, glucose, IGFBP-2, MIP-1 δ, MIP-3ß, NLR, RDW, Sgp130, and YKL-40.

Discussion

In this systematic review, we identified 415 different blood-based biomarkers that were tested in HGG patients for identification of their diagnostic utility with regard to differential diagnosis, prognosis, and postoperative monitoring. Based on the current level of evidence, we selected a panel of 10 biomarkers with the recently best positive evidence.

Biomarkers in Context of Modern Treatment of Cancer

The recent advances in the field of genomics, transcriptomics, proteomics, and metabolomics led to an intensified search for biomarkers, with special regard to cancer. Ideally, the biomarker can be measured objectively and thus facilitates early diagnosis and allows exclusion of potential differential diagnoses, helps to stratify the specific risk of a patient, estimates prognosis and the specific treatment response, and follows the course of disease longitudinally [14, 15]. Biomarkers, which can be detected in blood, carry the undeniable advantage to be minimally invasive and suitable even for patients in a poor clinical state. So far, only a few blood-based biomarkers are routinely applied for diagnosis, risk stratification, or monitoring of disease burden. Therefore, the prostate-specific antigen (PSA) serves as a screening method for prostate cancers but

suffers from limited specificity and a substantial rate of overdiagnosis. Still, there is a role for screening and monitoring using PSA for prostate cancer [16, 17]. Another example for a routinely implemented biomarker is S100B in malignant melanoma. Therefore, the European Society of Medical Oncology and the German Guidelines recommend serum S100B for follow-up of malignant melanoma, especially in advanced stages [6, 18]. In the light of the benefit and the very low risk-profile of blood-based biomarkers, there is a crucial need for further research on the field of biomarkers in cancer.

HGG Biomarkers: Diagnostic and Prognostic Value

The standard therapy for HGG comprises surgery, followed by concomitant chemotherapy and radiotherapy [19]. So far, follow-up work-up only consists of MRI studies and clinical examinations in regular intervals. Since almost every patient with HGG will suffer from recurrent disease, the estimation of patients' prognosis, tumor burden and risk profile is crucial for further treatment planning. So far, a biopsy with subsequent molecular testing is mandatory for the diagnosis and further stratification of HGG. In the light of restrictions for surgery, as multiple focal masses, higher age and poor clinical status, comorbidities and eloquent tumor locations, approximately 12% of patients only undergo diagnostic biopsy [20, 21]. Additionally, the procedure of surgery itself carries the risk for peri- and postoperative complications, which might lead to a lower probability to receive adjuvant therapies causing a shortened survival [22, 23]. Here, a blood-based biomarker or a panel of biomarkers predicting the tumor burden, the prognosis and risk profile of a patient could critically facilitate the decision-making. In the situation of a patient in a poor clinical state and a higher age, the patient could be spared of an unnecessary diagnostic surgery and be directly referred to less extensive therapies or best-supportive care. Therefore, biomarkers could help optimizing the choice and extent of applied therapies, leading to a better patient care.

Blood-Based Biomarkers for HGG Monitoring: a New Tool for Routine Use?

Alongside with radical tumor resection, optimal postoperative care is pivotal for HGG patients to prolong their survival. There are several diagnostic and logistic challenges in the monitoring of HGG patients after surgery. Especially in the situation of a potential tumor recurrence, the distinction between true progression and pseudo-progression using imaging modalities still may become confusing. Pseudo-progression occurs in approximately 20% of progressive cases after combined chemotherapy and radiotherapy [24–26] and is recently a matter of extensive research [27, 28]. Based upon our systematic review, none of the tested blood biomarkers is currently eligible for the differentiation between true progression and pseudo-progression of HGG.

Timely identification of tumor recurrence is another challenge of postoperative care in HGG patients. Disadvantages of magnetic resonance imaging with respect to lower availability and relative expensiveness, makes the application of routine blood tests for a short-term tumor monitoring potentially a cost-effective alternative. Therefore, blood-based HGG biomarkers, which are eligible for longitudinal measurements and address the above-mentioned diagnostic challenges, might become a helpful tool for timely recognition of disease progression and optimization of treatment strategies in HGG patients.

Detailed Description of the Most Promising Blood-Based Biomarkers

The following section describes the function of the identified biomarkers as also the methods of blood concentration detection.

AHSG

AHSG is an exosomal protein and is predominantly synthesized by liver parenchymal cells. It is involved in several physiological functions as inhibition of ectopic calcification and might play a role in tumor progression [29]. Serum concentration is maintained at approximately 0.5 mg/ml. For measurement of protein concentration, there are commercial kits that detect plasma level by ELISA [30, 31].

YKL-40

The exact function of YKL-40 is unknown. It is a heparin-chitin-binding glycoprotein without chitinase activity and is secreted among others by chondrocytes, synoviocytes, and vascular smooth muscle cells [32]. YKL-40 is overexpressed in several cancers, as breast cancer, osteosarcoma, and GBM. Serum level of YKL-40 can be determined by a commercial ELISA [33]. In healthy subjects, serum concentration is stable at low levels, there are no differences between genders and concentration increases in the elderly [34, 35].

IGFBP-2

IGFBP2 is a protein that binds insulin-like growth factors I and II. High protein levels of this protein promote the growth of several types of tumors [36]. Preoperative plasma level of IGFBP-2 was a significant prognostic factor in GBM patient, irrespective of their clinical status. Furthermore, plasma level increased after recurrence [37]. A commercial ELISA kit can measure plasma level and IGFPB-2 level did not vary with age and gender and during the day [37, 38].

SGP130

SGP130 protein specifically inhibits interleukin-6 (Il-6) trans-signaling but is involved in IL-6 classic signaling only at higher concentrations. Its cellular origin and mechanism are not understood [39]. Circulating levels of SGP130 can be determined by ELISA and are approximately 400 ng/ml. Increased levels can be observed with clinical events in patients with chronic heart failure [40].

MIP-1ð and MIP-3ß

MIP proteins are mainly produced by leucocytes after exposure to inflammatory cytokines and play a major role in recruitment of immune cells. MIP-1ð induces chemotaxis in immune cells and stimulates recruitment of osteoclast precursors and levels are significantly increased in bone metastasis [41]. MIP-3ß is thought to be involved in the development of chronic inflammation and lymphoid neogenesis [42].

Further Proteins

Serum levels of the other identified blood-based biomarkers like albumin, glucose, NLR, and RDW are influenced by several factors. The serum levels of these biomarkers are thought to be highly variable and are therefore prone to various biases.

General Limitations

There are several limitations with regard to the presented data. First, there might be a publication bias, as studies with negative reports are less likely to be published. Furthermore, the majority of included studies comprise only small cohorts of patients. In addition, impact of extrinsic (such as medication and technical aspects of biomarker analysis) and intrinsic (circadian rhythm) factors on serum levels of the tested biomarkers, and therefore, on the study results cannot be ruled out. Finally, many of the reviewed studies did not broach the issue of genetic heterogeneity in HGG. This aspect is recently of paramount significance in the present clinical management of HGG resulting in individualized treatment regimens.

Still, with emerging importance of genomics, transcriptomics, proteomics, and metabolomics, it is crucial to provide an overview of analyzed HGG biomarkers and to identify the most promising candidates for future validation.

Conclusions

Of 415 identified biomarkers, we selected 10 blood-based biomarkers as most promising biomarkers for HGG: AHSG, albumin, glucose, IGFBP-2, MIP-1δ, MIP-3ß, NLR, RDW, Sgp130, and YKL-40. To further assess the potential of these biomarkers, the evaluation in a larger cohort of HGG and their corresponding subgroups would be necessary.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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