**Background**

Cutaneous melanoma (CM) is one of the most lethal malignancies of skin [1]. It was estimated that 287,700 new cases of melanoma and 60,700 deaths of melanomas occurred worldwide in 2018 [2]. Patients with metastatic melanoma have a shorter long-term survival time. Moreover, survival outcomes can vary widely among patients even within the same stage due to the biological heterogeneity of melanoma. At present, the methods commonly used in the treatment of melanoma include surgical resection, chemotherapy and immunotherapy. Only a few patients with advanced melanoma have a persistent response to surgical resection and chemotherapy. Some researchers have used mouse models to analyze the causes of drug resistance, possibly due to changes in metabolic levels in...
the state of obesity [3, 4]. Weight control can improve the effectiveness of medications and help reduce melanoma metastasis [5]. In addition, the combination of chemotherapy drugs may improve drug resistance [6, 7]. However, because of the molecular heterogeneity, not all the melanoma patients responded well to the treatments. Mutant BRAF has been shown to be significantly associated with worsen overall survival and metastasis free survival of melanoma [8], meanwhile mutant BRAF has been also proven to be a good therapeutic target for melanoma, but the resistance of small molecule drugs against mutant BRAF for melanoma is invariably observed [9]. Therefore, it is imperative to develop novel prognostic biomarkers for risk stratification and treatment optimization in melanoma patients. The specific and novel biomarker may provide the opportunities for guidance of personalized therapeutic interventions and new therapeutic target development.

High-throughput RNA-sequencing (RNA-Seq) has been shown to successfully measure gene expression, discover novel transcripts and identify differentially expressed genes [10]. BRAF and NRAS mutations have been used as molecular biomarkers in evaluating the clinical course of melanoma. Identification of novel molecular biomarkers becomes an area of interests to clinicians and researchers. Ideally, prognostic biomarkers are sensitive, specific, reliable, rapidly analyzable and cost effective. To date, a number of prognostic biomarkers have been proposed in melanoma [11]; however, most of these putative biomarkers lack independent validation in multiple cohorts. Mining available transcriptome data with appropriate clinical follow-up information offers opportunities to prescreen and validate new prognostic biomarkers [12]. Currently, there are several web-browsers, such as PRECOG [13], KM plotter [14] and CaPSSA [15], which have provided survival analysis based on gene expression. However, most of these prognostic analysis web servers only provide data from TCGA, without data from other sources such as GEO and published literatures. As we all know, the most important and difficult part of the biomarker development is to validate the performance of potential biomarker in multiple independent datasets, in this current study, we developed an Online consensus Survival webserver for Skin Cutaneous Melanoma, named OSskcm, which analyzes tumor gene expression profiles and clinical follow-up information of 1085 melanoma patients from multiple independent cohorts. The OSskcm webserver is registration-free and can assist biologists and clinicians to evaluate the prognostic potency of genes of interests and identify potential therapeutic targets.

Materials and methods
Expression profiling and clinical follow-up data used in OSskcm were collected from Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) and The Cancer Genome Atlas (TCGA; https://cancergenomeme.nih.gov/) by searching with the keywords of “cutaneous melanoma” and “survival”. Only datasets containing mRNA expression profiling data, clinical survival information, and at least 20 cutaneous melanoma cases were included. The Kaplan–Meier (KM) survival curves were set up using a central server, Hazard ratio (HR) and 95% confidence interval (95%CI) were calculated in a univariate Cox regression analysis. Risk factors, including race, stage, gender, age and type of therapy, can be selected for a subgroup analysis. The OSskcm is hosted in a windows tomcat server. Server-side scripts were developed in Java script, which control the request of analysis and return the analysis results. The database system is managed by a SQL Server, which integrates gene expression data and clinical data. The central server for OSskcm can be accessed at http://bioinfo.henu.edu.cn/Melanoma/MelanomaList.jsp. More details of the methods of OSskcm development have been described [16–19].

Results
Clinical characteristics of cutaneous melanoma cohorts in OSskcm
We collected 1085 unique patients, including 615 patients from six GEO datasets and 470 patients from TCGA dataset. These melanoma samples include 221 primary cutaneous melanomas, 851 metastatic melanomas, and the tumor origin of 13 patients was unknown. (Table 1). The median age of patients is 59 years old. 762 patients have overall survival (OS) data, and the median overall survival is 39.3 months. In addition, 475 patients have progression-free survival (PFS) data, 665 patients have disease-specific survival (DSS) data, 470 patients have progression-free interval (PFI) data, and 150 patients have distant metastasis-free survival (DMFS) data.

The application of OSskcm webserver
To apply OSskcm to determine the prognostic value of gene of interest, users only need to input an official gene symbol into “Gene symbol” dialog box, and choose “Data source” as either one individual dataset or combined datasets, then select one of the “Survival” terms such as OS, PFS, DSS or PFI, and select a appropriate cut-off value of gene expression stratification by “Split patients by”. After then click the ‘Kaplan–Meier plots’ button, the KM plots with log-rank P value and HR with 95%CI will be shown on the output web page (Fig. 1). If users are interested in the prognostic
significance of biomarkers in a particular subgroup of patients, such as races, tumor stages and treatment methods, they may select corresponding risk factors to filter the patients prior to Kaplan–Meier analysis.

Validation of previously published cutaneous melanoma biomarkers

A PubMed search was performed using keywords of ‘cutaneous melanoma’, ‘survival’, and ‘biomarker’ to identify genes previously reported as prognostic biomarkers for cutaneous melanoma in the literatures. In total, 30 such prognostic genes were validated in OSskcm (listed in Table 2). These biomarker candidates were generally detected by tissue-based immunohistochemistry or immunofluorescent staining.

The analysis of these reported prognostic biomarkers in OSskcm showed that the prognostic roles of 22 genes were consistent with previous findings, RBM3 gene had no statistically significance on prognosis, and the other 7 genes (KLK7, CXCR4, CDKN1B, BCL6, CTNNB1, RUNX3 and DDIT3) had opposite prognostic trends compared to literatures. The analysis results were presented in Table 2.

Screening of new prognostic biomarkers for cutaneous melanoma

OSskcm can also be used to screen novel prognostic biomarkers for cutaneous melanoma, where OS, DSS, PFS, PFI and DMFS can be investigated. By OSskcm, we found that high expression of SAE1 gene is associated with poor prognosis of cutaneous melanoma (Fig. 2), and the prognostic potency of SAE1 gene has not been previously reported in cutaneous melanoma.

Discussion

Due to the variant prognosis of cutaneous melanoma patients, the development of molecular prognosis biomarkers is significant. Here, we collected multiple large transcriptomic datasets to increase the statistical power for analyzing the association between the investigated marker and survival rate, and developed a freely accessible webserver OSskcm to estimate the prognostic value of any inputted gene in a large cohort of patients, by which KM survival curves as well as HR and log-rank P values could be outputted and presented. OSskcm is a webserver that can mutually validate prognostic biomarkers of cutaneous melanoma in multiple data sets. A total of 1085 patients of cutaneous melanoma with RNA-seq data from clinical tissues and clinical information were included in OSskcm. In addition, risk factors, including race, stage, gender, age and therapy type, can be selected for subgroup analysis. Clinical outcome data of OS, PFS, DSS, PFI, and DMFS was included in analysis.

We tested the performance of OSskcm using 30 previously reported cutaneous melanoma prognostic biomarkers. Among these, 22 genes were validated in OSskcm, but the prognostic significance of RBM3, KLK7, CXCR4, CDKN1B, BCL6, CTNNB1, RUNX3 and DDIT3 genes was inconsistent between literatures and OSskcm. It may be because the OSskcm utilizes mRNA expression data while all previously published biomarkers

### Table 1 Clinical properties of cutaneous melanoma patients in OSskcm

| GEO ID   | References | Platform | No. of samples | Death event | Median overall survival (months) | Ages (years) | Gender (male/female) | Primary/metastatic | Stage (I/II/III/IV) |
|----------|------------|----------|----------------|-------------|---------------------------------|--------------|---------------------|-------------------|-------------------|
| GSE17275 | [20]       | GPL1930  | 60             | 41          | 64.00 (46.25–89.50)             | NA           | NA                  | 20/40             | 2/8/19/31         |
| GSE22155 | [21]       | GPL6102  | 70             | 60          | 7.27 (2.10–13.80)               | 56.63±14.58  | 39/31               | 0/70              | 0/0/3/67          |
| GSE46517 | [22]       | GPL96    | 84             | 40          | 71 (55–89)                      | 77.03±26.37  | 39/24               | 31/53             | 12/15/11/24       |
| GSE50509 | [23]       | GPL10515 | 19             | 15          | 18.11 (8.63–26.53)              | 57.68±15.49  | 12/7                | 0/19              | NA                |
| GSE65904 | [24]       | GPL10558 | 214            | 102         | 72.08 (7.03–41.83)              | 62.35±14.40  | 124/89              | 16/188            | NA                |
| GSE98394 | [25]       | GPL16791 | 51             | 18          | 93.50 (35.00–111.00)            | NA           | 31/20               | 51/0              | 12/22/10/0       |
| GSE19234 | [26]       | GPL570   | 38             | 24          | 38.08 (23.57–65.90)             | 62.66±17.86  | 24/14               | 0/38              | 0/0/34/4         |
| GSE53118 | [27]       | GPL6884  | 79             | 47          | 79.74 (28.81–120.05)            | 55.49±15.27  | 50/29               | 0/79              | 0/0/79/0         |
| TCGA      | [28]       | Illumina | 470            | 216         | 34.45 (14.90–75.17)             | 58.22±15.73  | 290/180             | 103/364           | 77/140/171/23    |
| Total     |            |          | 1085           | 563         | 39.30 (15.92–88.00)             | 59.14±15.55  | 609/394             | 221/851           | 131/215/268/149 |

NA not available

a The survival endpoint was defined as event-free survival from resection until death

b The survival endpoint was defined as disease-specific survival

c Partial data missing

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[Table 1 clinical properties of cutaneous melanoma patients in OSskcm](#)
were studied based on the protein level. It is known that there is an inconsistency between the levels of mRNA and protein due to intracellular modifications, such as post-transcriptional regulation, protein translation and post-translational regulation. In addition, the prognostic significance of a protein may be determined by its subcellular localization. For example, loss of nuclear CDKN1B expression is correlated with a worse 5-year survival of primary melanoma patients in Kaplan–Meier analysis, but gain of cytoplasmic CDKN1B was associated with a poor 5-year survival of metastatic melanoma patients.

*KIF20A* and *RGS1* genes have been reported to play critical roles in the development and progression of cancer, and promote the proliferation, migration and invasion of cancer cells [58, 59]. In OSkcm, *KIF20A* and *RGS1* were found to be strongly associated with cutaneous melanoma prognosis. In addition, we found that *SAE1* could be a new prognostic biomarker in cutaneous melanoma. *SAE1* is dimeric SUMO Activating Enzyme E1, involved in SUMO conjugation [60]. Breast cancer patients with lower *SAE1* expression have been reported to have significantly lower instances of metastatic cancer and increased survival compared to those that express a higher level of *SAE1* [61]. Moreover, *SAE1* was reported to have the strongest synthetic lethal interactions with K-Ras and can be used to evaluate the aggressiveness of mutated K-Ras-dependent malignancies [62]. It will be interesting to further verify by

Fig. 1 The usage and output web page of OSkcm webserver
Table 2 Performance of previously published protein prognostic biomarker candidates in OSskcm

| Gene symbol | Literature data | Validation results |
|-------------|-----------------|-------------------|
|             | References      | Survival endpoint | Prognostic significance of high expression | HR (95%CI) | Log-rank P value | Datasets | Cut off |
| KLK7        | [20]            | OS                | Good | 2.65 (1.27–5.53)† | 0.0095 | GSE17275 | Upper 25% |
|             |                 | RFS               | Poor | 3.60 (1.48–8.80)† | 0.0049 | GSE19234 | Upper 25% |
| MITF        | [29]            | OS                | Poor | 1.93 (1.40–2.65)† | < 0.0001 | TCGA | Upper 25% |
|             |                 | OS                | Poor | 1.43 (1.09–1.87)† | 0.0104 | TCGA | Upper 50% |
|             |                 | OS                | Poor | 3.46 (1.42–8.42)† | 0.0063 | GSE19234 | Upper 50% |
|             |                 | OS                | Poor | 3.33 (1.18–9.41)† | 0.0230 | GSE98394 | Upper 50% |
| KIF20A      | [30]            | RFS               | Poor | 2.17 (1.12–4.20)† | 0.0218 | GSE22155 | Upper 25% |
|             |                 | RFS               | Poor | 2.56 (1.20–5.47)† | 0.0151 | GSE9509 | Upper 25% |
|             |                 | RFS               | Poor | 3.21 (1.26–8.20)† | 0.0147 | GSE98394 | Upper 25% |
|             |                 | RFS               | Poor | 2.44 (1.02–5.83)† | 0.0454 | GSE19234 | Upper 25% |
| CTHRC1      | [31]            | OS                | Poor | 3.41 (1.31–8.89)† | 0.0122 | GSE98394 | Upper 25% |
| TFAP2A      | [32]            | DSS               | Poor | 1.59 (1.03–2.47)† | 0.0379 | GSE65904 | Upper 25% |
| ATP2        | [33]            | OS                | Poor | 3.05 (1.56–5.97)† | 0.0012 | GSE22155 | Upper 25% |
| NCOA3       | [34]            | RFS and DSS       | Poor | 1.79 (1.17–2.74)† | 0.0071 | GSE65904 | Upper 25% |
| BCL2        | [35]            | OS                | Good | 0.21 (0.04–0.97)† | 0.0458 | GSE22155 | Upper 25% |
| BIRC5       | [36]            | OS                | Poor | 3.73 (1.44–9.67)† | 0.0068 | GSE98394 | Upper 25% |
| MCAM        | [37]            | OS                | Poor | 4.66 (1.78–12.18)† | 0.0017 | GSE19234 | Upper 25% |
| PLAT        | [38]            | DMFI and OS       | Poor | 2.24 (1.16–4.34)† | 0.0164 | GSE22155 | Upper 25% |
| NOS2        | [39]            | DSS and OS        | Poor | 3.88 (1.47–10.24)† | 0.0063 | GSE98394 | Upper 25% |
| CDKN1B      | [40]            | DSS and OS        | Poor | 1.41 (0.71–2.85)† | 0.0313 | TCGA | Upper 50% |
|             |                 | DSS and OS        | Poor | 0.48 (0.24–0.95)† | 0.0341 | GSE22155 | Upper 25% |
| BCL6        | [41]            | 6-year OS         | Poor | 0.69 (0.50–0.95)† | 0.0235 | TCGA | Upper 25% |
| FXYD5       | [42]            | OS                | Poor | 0.57 (0.40–0.80)† | 0.0011 | TCGA | Upper 25% |
| DDIT3       | [43]            | OS                | Poor | 3.10 (1.24–7.76)† | 0.0159 | GSE19234 | Upper 25% |
| MCAT        | [44]            | OS                | Good | 5.74 (2.18–15.13)† | 0.0004 | GSE98394 | Upper 25% |
| CTNNB1      | [45]            | DSS               | Good | 5.75 (1.26–26.10)† | 0.0236 | GSE22155 | Upper 25% |
| AKT1        | [46]            | 5-year DSS or OS  | Poor | 1.55 (1.02–2.37)† | 0.0412 | GSE65904 | Upper 25% |
| RUNX3       | [47]            | 5-year OS         | Good | 1.75 (1.15–2.67)† | 0.0088 | GSE65904 | Upper 25% |
|             |                 | 5-year DSS        | Good | 1.53 (1.13–2.06)† | 0.0056 | TCGA | Upper 25% |
| BBC3        | [48]            | 5-year DSS or OS  | Poor | 3.75 (1.36–10.33)† | 0.0107 | GSE50509 | Upper 25% |
| MMP2        | [49]            | DSS and RFS       | Poor | 1.81 (1.18–2.76)† | 0.0062 | GSE65904 | Upper 25% |
| SPP1        | [50]            | RFS               | Poor | 3.62 (1.38–9.52)† | 0.0092 | GSE98394 | Upper 25% |
| TNC         | [51]            | DFS               | Poor | 3.10 (1.24–7.76)† | 0.0159 | GSE19234 | Upper 25% |
| CCNA2       | [52]            | RFS               | Poor | 2.33 (1.02–4.88)† | 0.0437 | GSE50509 | Upper 25% |
| RGS1        | [53]            | DSS               | Poor | 2.74 (1.03–7.24)† | 0.0425 | GSE98394 | Upper 25% |
| SPARC       | [54]            | DFS               | Poor | 3.24 (1.31–8.00)† | 0.0110 | GSE19234 | Upper 25% |
| CXOR4       | [55]            | DFS and OS        | Poor | 2.66 (1.07–6.65)† | 0.0357 | GSE19234 | Upper 25% |
| RBM3        | [56]            | OS                | Good | 2.78 (1.21–6.34)† | 0.0154 | GSE50509 | Upper 25% |
| EPH5J1      | [57]            | DFS               | Poor | 0.70 (0.51–0.97)† | 0.0315 | TCGA | Upper 25% |
|             |                 | OS                | Good | NS | NS | – – |

‡ Not significance, RFS recurrence-free survival, DFS disease-specific survival, DFI disease-free interval, DMFI distant metastasis-free interval

†,‡ HR (95%CI) and Log-rank P value of overall survival (OS) and disease-specific survival (DSS)
experiments whether SAE1 gene could be a new prognostic biomarker in cutaneous melanoma.

**Conclusion**

In summary, by utilizing genome-wide microarray datasets and RNAseq datasets, we built a prognosis webserver, OSskcm, which offer a platform for biologists and clinicians to identify prognostic biomarkers for cutaneous melanoma. Additional more research regarding how to better translate our webserver and web server derived biomarkers for practice from local to global health is required [63].

**Abbreviations**

OSskcm: Online consensus Survival webserver for Skin Cutaneous Melanoma; GEO: Gene Expression Omnibus; TCGA: The Cancer Genome Atlas; OS: Overall survival; PFS: Progression-free survival; DSS: Disease-specific survival; PFI: Progression-free interval; DMFS: Distant metastasis-free survival; DFS: Disease-specific survival; DFI: Disease-free interval, DMFI: Distant metastasis-free interval.

**Fig. 2** SAE1 is identified as an unfavorable prognostic biomarker in OSskcm. Overall survival (OS) curve of cutaneous melanoma patients based on TCGA (a), GSE19234 (b), GSE22155 (c) and GSE98394 (d) data. Upper 25%: the SKCM cases with ranked top 25% higher expression level for the inputted gene; Other 75%: the SKCM cases with ranked bottom 75% lower expression level of the inputted gene.

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**Authors’ contributions**

All authors materially participated in the study and manuscript preparation. XQG, LZ and QW participated in the design and the conception of the study. LJW, ZHL, XCZ, PPT and XZH collected and managed data. XQG, LZ and QW developed methods and performed data analysis. QW built the webserver. YQL provided technical support. LZ and QW wrote the original draft. LXX, YA, GSZ, WZ and XQG reviewed and edited the manuscript. XQG supervised the research process. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) and The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/).
Ethics approval and consent to participate
Not applicable.

Consent for publication
We have obtained consents to publish this paper from all participants of this study.

Competing interests
The authors declare that they have no competing interests.

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