

RESEARCH ARTICLE

Open Access



Prognostic significance of autophagy-related genes within esophageal carcinoma

Chongxiang Chen^{1,2†}, Siliang Chen^{3†}, Huijiao Cao^{4†}, Jiaojiao Wang⁵, Tianmeng Wen⁶, Xiaochun Hu^{3*} and Huan Li^{1*}

Abstract

Background: Several works suggest the importance of autophagy during esophageal carcinoma development. The aim of the study is to construct a scoring system according to the expression profiles of major autophagy-related genes (ARGs) among esophageal carcinoma cases.

Methods: The Cancer Genome Atlas was employed to obtain the esophageal carcinoma data. Thereafter, the online database OncoPrint (<http://www.oncoPrint.org/>) was employed to verify the accuracy of our results. According to our results, the included ARGs were related to overall survival (OS).

Results: We detected the expression patterns of ARG within esophageal carcinoma and normal esophageal tissues. In addition, we identified the autophagy related gene set, including 14 genes displaying remarkable significance in predicting the esophageal carcinoma prognosis. The cox regression results showed that, 7 ARGs (including TBK1, ATG5, HSP90AB1, VAMP7, DNAJB1, GABARAPL2, and MAP2K7) were screened to calculate the ARGs scores. Typically, patients with higher ARGs scores were associated with poorer OS. Moreover, the receiver operating characteristic (ROC) curve analysis suggested that, ARGs accurately distinguished the healthy people from esophageal carcinoma patients, with the area under curve (AUC) value of > 0.6.

Conclusion: A scoring system is constructed in this study based on the main ARGs, which accurately predicts the outcomes for esophageal carcinoma.

Keywords: Esophageal carcinoma, Autophagy, Prognostic

Background

Nowadays, studies around the world show that, esophageal carcinoma ranks the 7th and 6th places in terms of its morbidity tumor-related mortality cause [1]. However, the area distribution is imbalanced between cases and deaths,

and some areas are regarded as the “esophageal carcinoma belt” [2, 3]. Several factors, such as smoking, obesity, low vegetable consumption, have been proven to adversely predict esophageal carcinoma [4, 5]. Nowadays, an increasing obesity trend in western countries results in the further increased esophageal carcinoma morbidity [1], as proven in one meta-analysis [6].

So far, several prognostic studies have used various indicators (including PET-CT [7], HER2 [8], Microsatellite instability [9] and PD-L1 expression [10]) to predict the long-term outcomes, and other studies have evaluated the treatment efficacy, or complications among esophageal carcinoma patients [11, 12].

* Correspondence: huxch@sysucc.org.cn; lihuan@sysucc.org.cn

[†]Chongxiang Chen, Siliang Chen and Huijiao Cao contributed equally to this work.

³Department of hematology, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

¹Department of Intensive Care Unit, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng Dong Road, Guangzhou 510060, People's Republic of China

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Autophagy, a crucial biological process, balances the homeostasis in cells through the degradation of injured or aged organelles and proteins within lysosomes [13, 14]. Previous studies have validated the role of autophagy in promoting tumor cell survival and suppressing oncogenesis [15–17]. On this account, both enhancing and inhibiting autophagy have been suggested as the treatment strategies [18–21], which suggest that patient assessment plays an important role in autophagy. A large number of studies demonstrate that autophagy activation shows marked correlation with the tumor dormancy, chemoresistance, as well as stem cell survival [22].

According to previous studies, autophagy is correlated with esophageal carcinoma diagnosis and treatment [23]. However, the role of autophagy in the

prognosis for esophageal carcinoma has scarcely been assessed by large-scale expression data. Therefore, this study was designed to construct a novel scoring system based on the screened important ARGs, which might contribute to a perspective tool in evaluating patient prognosis.

Methods

Autophagy related gene set

We identified autophagy related genes in human autophagy database.

Patient samples

Both clinical data and gene expression patterns of esophageal carcinoma were retrieved based on The Cancer Genome Atlas (TCGA) database. Ultimately, a

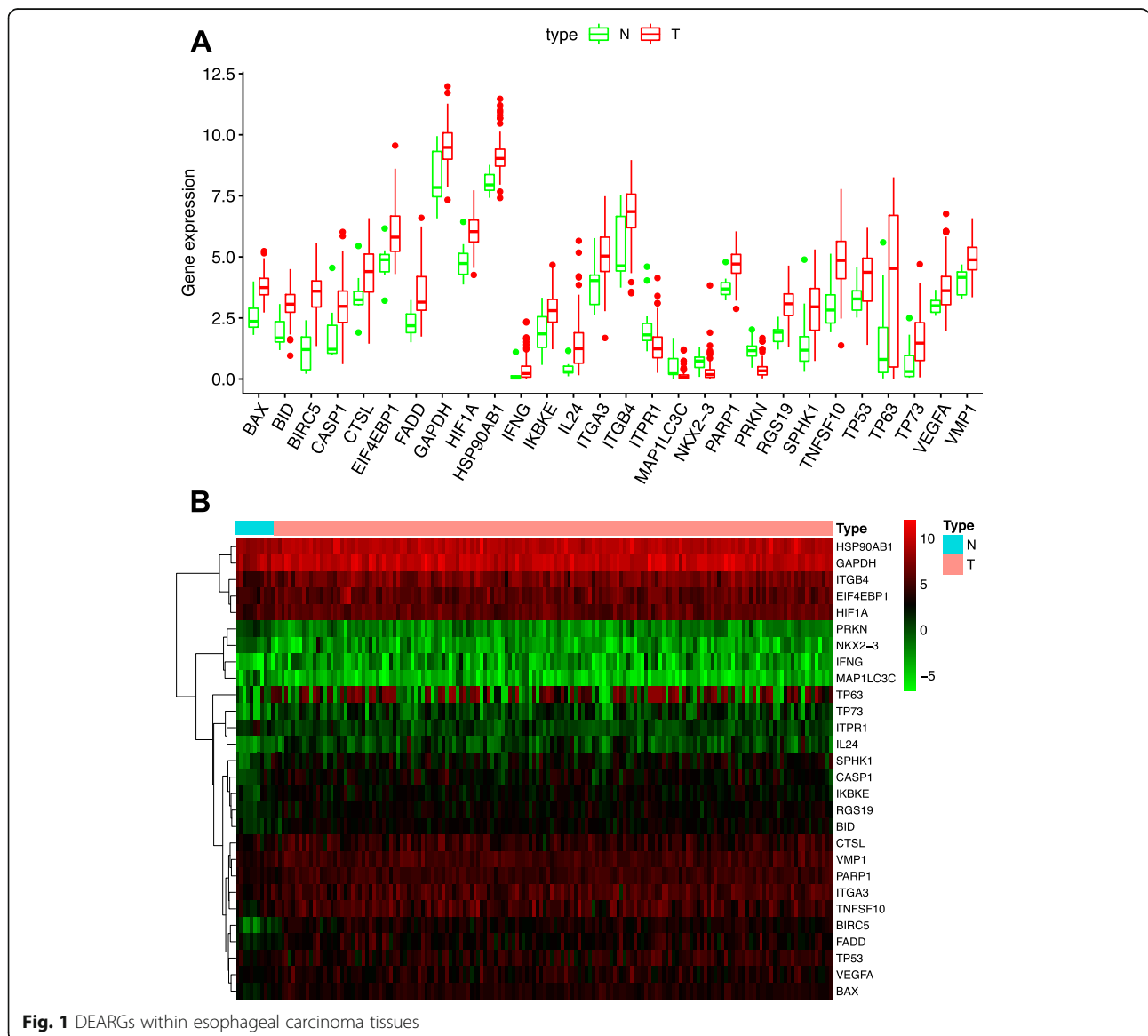


Fig. 1 DEARGs within esophageal carcinoma tissues

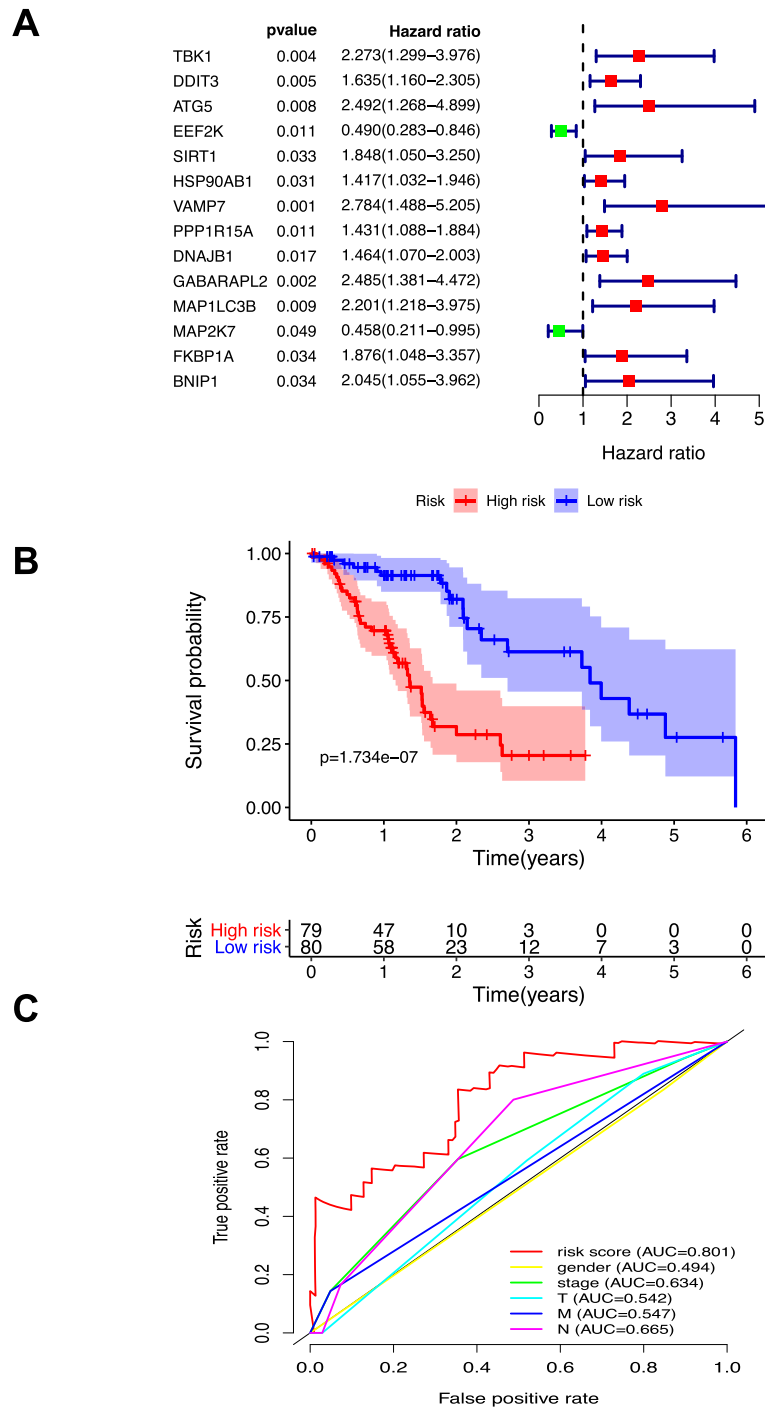


Fig. 2 ARGs within patients with esophageal carcinoma were used to construct and analyze the risk models for OS. **a** ARGs expression among esophageal carcinoma cases was analyzed through univariate Cox regression analysis **b** OS for esophageal carcinoma cases with low (green line) and high (red line) risk was analyzed by Kaplan-Meier survival curve. **c** ROC curves showing the values of AUC for OS among esophageal carcinoma cases

total of 171 specimens were collected based on TCGA microarray to be the cohort.

Processes

First, we carried out Principal component analysis (PCA) using R program to investigate those different expression profiles of genes in the enrolled specimens. Second, we plotted the receiver-operating characteristics (ROC) curves using the survival ROC of R package to assess the survival specificity and sensitivity. Then, we determined the values of area under the ROC curve (AUC) based on those plotted ROC curves. Last, we used the online database OncoPrint to prove the accuracy of our results.

Statistical analyses

Multivariate and univariate Cox regression analyses were carried out to assess the correlation among ARGs, the risk score value (based on ARGs) and other clinical characteristics in prognosis prediction. Based on the risk score, patients with esophageal carcinoma were divided into low- and high-risk group according to the median score. The results of survival analyses were recognized as the key outcomes; and Kaplan-Meier analysis was used to analysis the patient prognosis (OS) among various ranges of score. The time-dependent ROC curves were plotted to calculate the risk model predictive ability. R software (version 3.6.1) was used to make Bioinformatic analyses. $P < 0.05$ was regarded as statistically significant. χ^2 test or Student's t-test was used to analysis the differences of clinical baseline characteristics between low-risk and high-risk group.

Results

Differentially expressed ARGs (DEARGs) within esophageal carcinoma tissues

Wilcoxon signed-rank test was carried out to analyze the 232 ARGs expression within 11 normal esophageal and 160 esophageal carcinoma samples, and 28 DEARGs were found, including 24 up-regulated and 4 down-regulated ones ($|\log_2FC| > 1$, $FDR < 0.05$, Fig. 1). Figure 1a was box plot of 28 DEARGs (red boxes showed the genic expression of tumor sample, and green boxes indicated the genic expression of normal sample); and Fig. 1b was the heat map of 28 DEARGs (red indicated higher expression and green indicated lower expression).

Prognostic factor of DEARGs among esophageal carcinoma patients

Univariate Cox regression analysis was performed to examine ARGs expression within esophageal carcinoma cases, for the sake of identifying the significance of

ARGs in prognosis prediction. According to our results, TBK1, ATG5, HSP90AB1, VAMP7, DNAJB1, GABARAPL2, and MAP2K7 expression was remarkably related to patient OS ($P < 0.05$). (Fig. 2a).

To identify the best signature to in prognosis prediction, multivariate Cox proportional hazards regression analysis was further carried out. As suggested by our results, TBK1 (HR 1.877, 95%CI 0.985–3.574), ATG5 (HR 2.913, 95%CI 1.464–5.795), HSP90AB1 (HR 1.449, 95%CI 1.005–2.087), VAMP7 (HR 2.712, 95%CI 1.310–5.614), DNAJB1 (HR 1.688, 95%CI 1.255–2.270), GABARAPL2 (HR 2.853, 95%CI 1.585–5.136), and MAP2K7 (HR 0.510, 95%CI 0.217–1.199) were identified as the independent adverse prognostic factors. The risk score calculating formula was $(0.6295 \times TBK1 \text{ expression}) + (1.0691 \times ATG5 \text{ expression}) + (0.3706 \times HSP90AB1 \text{ expression}) + (0.9976 \times VAMP7 \text{ expression}) + (0.5236 \times DNAJB1 \text{ expression}) + (1.0485 \times GABARAPL2 \text{ expression}) - (0.6739 \times MAP2K7 \text{ expression})$.

Higher ARGs score was related to the worse OS

Table 1 displays the baseline characteristics of all included patients. As suggested by our log-rank test results

Table 1 Baseline characteristics of patients with esophageal carcinoma

Characteristics	Variable	Total (183)	Percentages (%)
Gender	Female:	27	14.75%
	Male:	156	85.25%
Stage	Stage I	18	9.83%
	Stage II	78	42.62%
	Stage III	55	30.05%
	Stage IV	9	4.92%
	Unknown	23	12.57%
T	T0	1	0.55%
	T1	31	16.94%
	T2	43	23.50%
	T3	86	46.99%
	T4	5	2.73%
	Unknown	17	9.29%
M	M0	134	73.22%
	M1	9	4.92%
	Unknown	40	21.86%
N	N0	76	41.53%
	N1	68	37.16%
	N2	12	6.56%
	N3	8	4.37%
	Unknown	19	10.38%
Survival rate	Survival	74	40.44%
	Death	109	59.56%

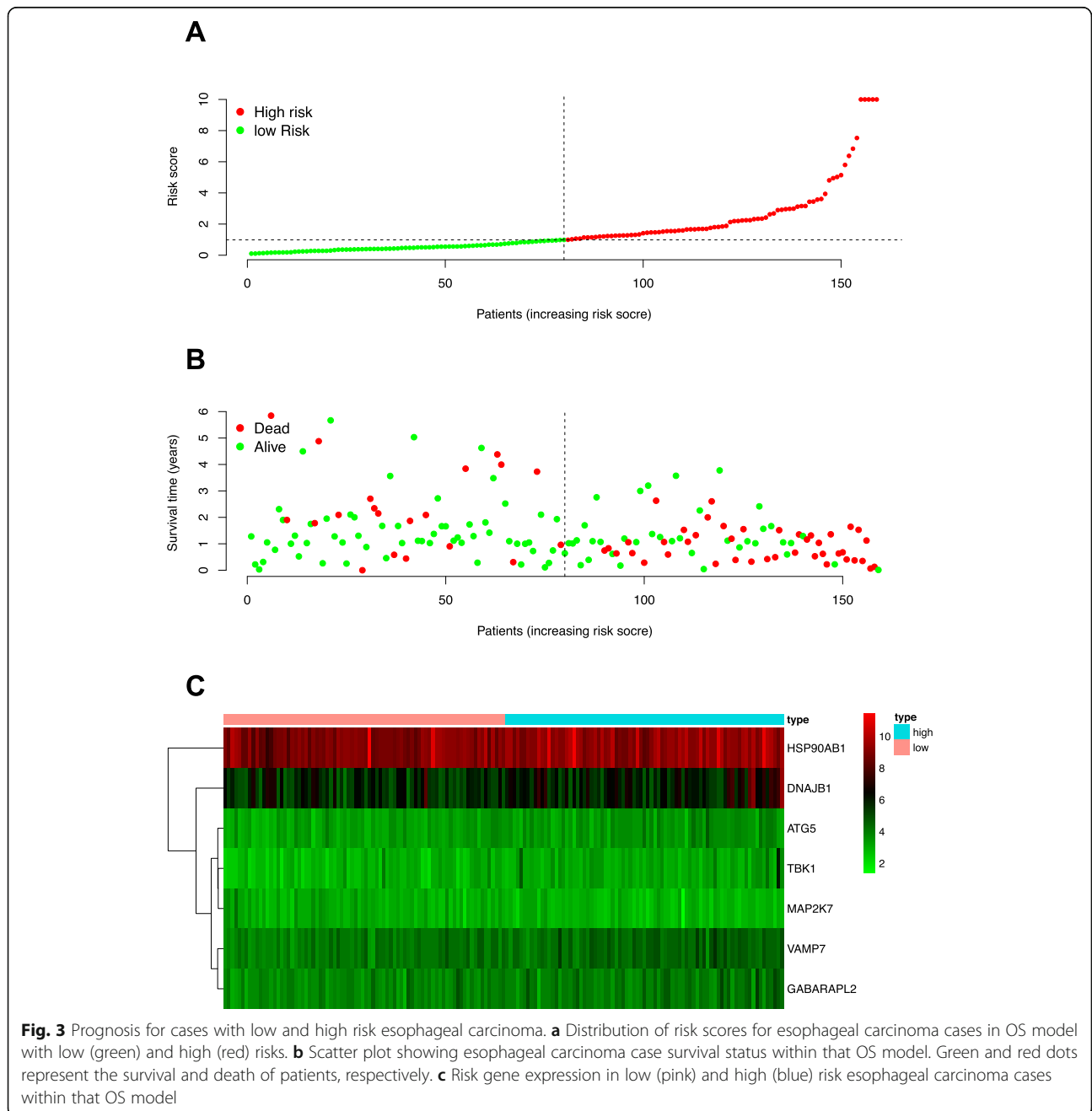
obtained using the Kaplan-Meier survival curve, compared with low-risk cases, the high-risk cases showed poor prognosis (Fig. 2b).

Then, the ROC curves were plotted to determine the effect of that as-constructed signature on predicting patient OS. As suggested by our results, the value of AUC was 0.801 for those prognostic models to predict OS, which was greater than that of gender (AUC = 0.494), stage (AUC = 0.634), T (AUC = 0.542), N (AUC = 0.665), and M (AUC = 0.547). Afterwards, the distributions of patient OS

risk scores were ranked and examined (Fig. 3). To better predict the clinical outcomes for patients with esophageal carcinoma, baseline characteristics (including gender, tumor, node, and metastasis stage in every patient) were incorporated into ROC curve analysis (Fig. 2c).

Gene Ontology (GO) functional enrichment analysis

The above-mentioned genes with prognostic significance were extracted for functional enrichment analysis. According to the top 10 most significant GO terms with



regard to MF, CC and BP categories, the above-mentioned ARGs were potentially related with ARGs regulation. (Fig. 4).

Multivariate cox regression analysis on risk score together with baseline clinical features

As suggested by the findings, only risk score (HR 1.271 95%CI 1.176–1.372) was the independent risk factor for the worse OS. (Fig. 5) Fig. 5a indicated the results of univariate cox regression analysis, and Fig. 5b showed the results of multivariate cox regression analysis.

Associations among the risk scores, ARGs, and clinical status (including survival, gender, age, stage, T, N, and M stage)

The results indicated that HSP90AB1, VAMP7, and risk score were related to the survival status and gender. In addition, GABARAPL2 was markedly associated with the survival status and stage. (Fig. 6).

The online database OncoInc (<http://www.oncolnc.org/>) was used to test the included ARGs

The high-risk ARGs were correlated with poor prognosis; however, the low-risk DEARGs showed

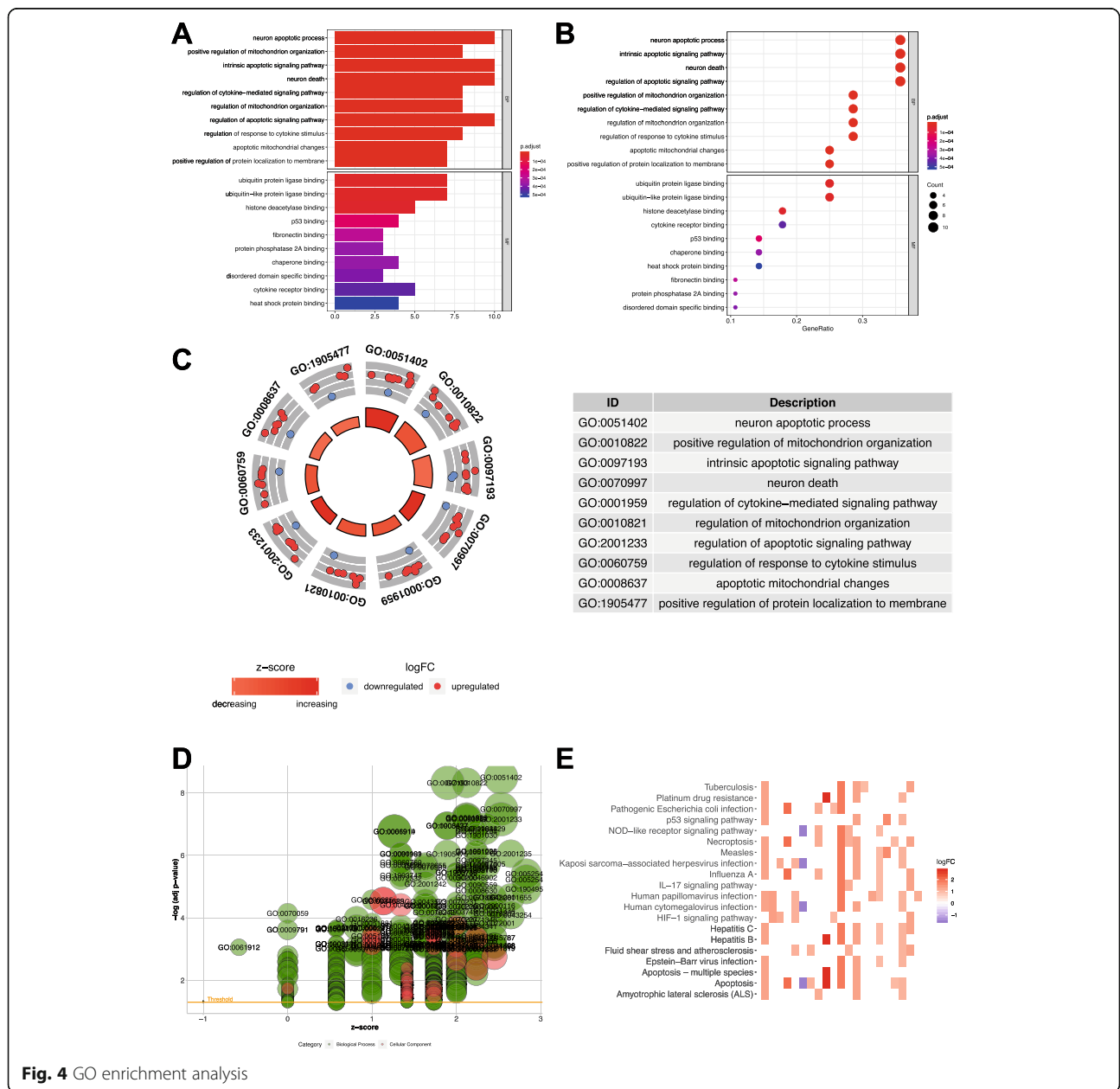


Fig. 4 GO enrichment analysis

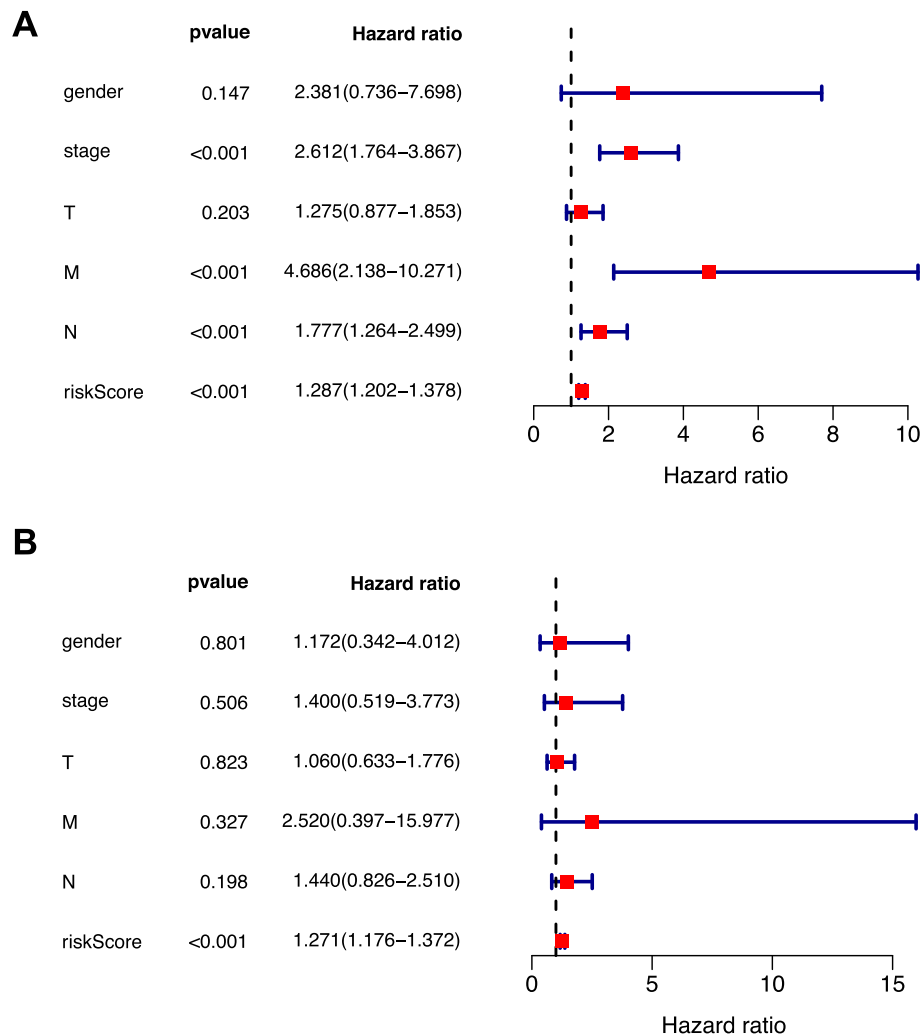


Fig. 5 Multivariate and univariate Cox regression analyses for OS among esophageal carcinoma cases. **a-b** univariate and multivariate cox regression analyses, respectively

significant association with favorable patient prognosis. (Fig. 7).

Discussion

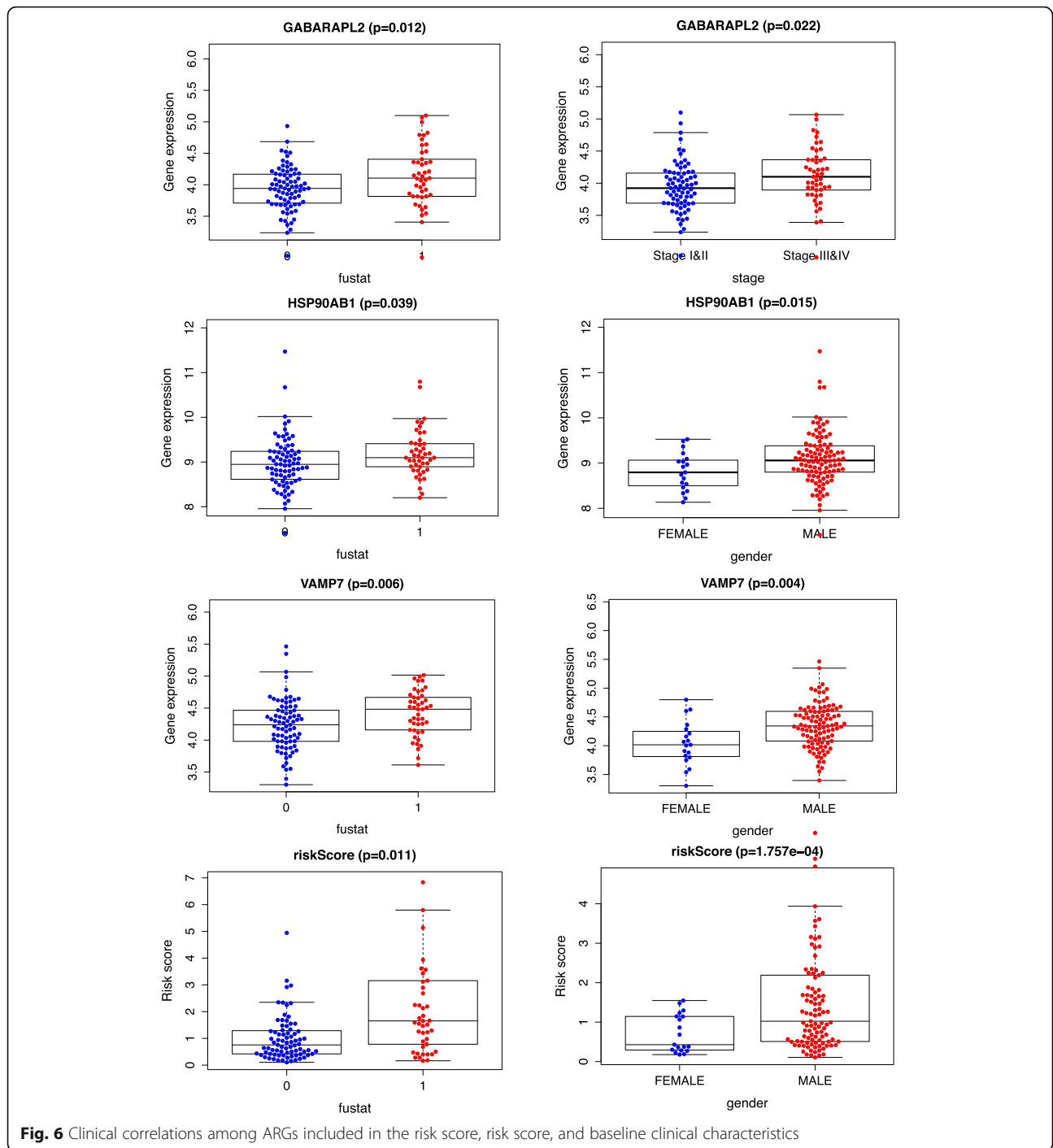
Histologically, esophageal carcinoma can be classified as adenocarcinoma and squamous cell carcinoma [24]. This study included both esophageal cancer subtypes to develop a more helpful tool for predicting the prognosis for esophageal carcinoma. Obviously, the risk score calculated by ARGs demonstrated superiority to other classical clinical indicators, and it was also the independent risk factor for patient survival.

In physiological situation, autophagy, which serves as a crucial catabolic process, works as an intracellular quality control system to maintain internal environment homeostasis through removing the damaged proteins [25]. However, autophagy has been proven to play an important role in various disorders,

including cancer, degradation, autoimmune disease and inflammation [23]. During cancer development, autophagy promotes cancer cell survival within various environments [26, 27]. As the new therapeutic approach, the mechanism of autophagy in tumor has long been proposed. Even, Sui et al. [28] pointed that autophagy was necessary for responses to chemoradiotherapy.

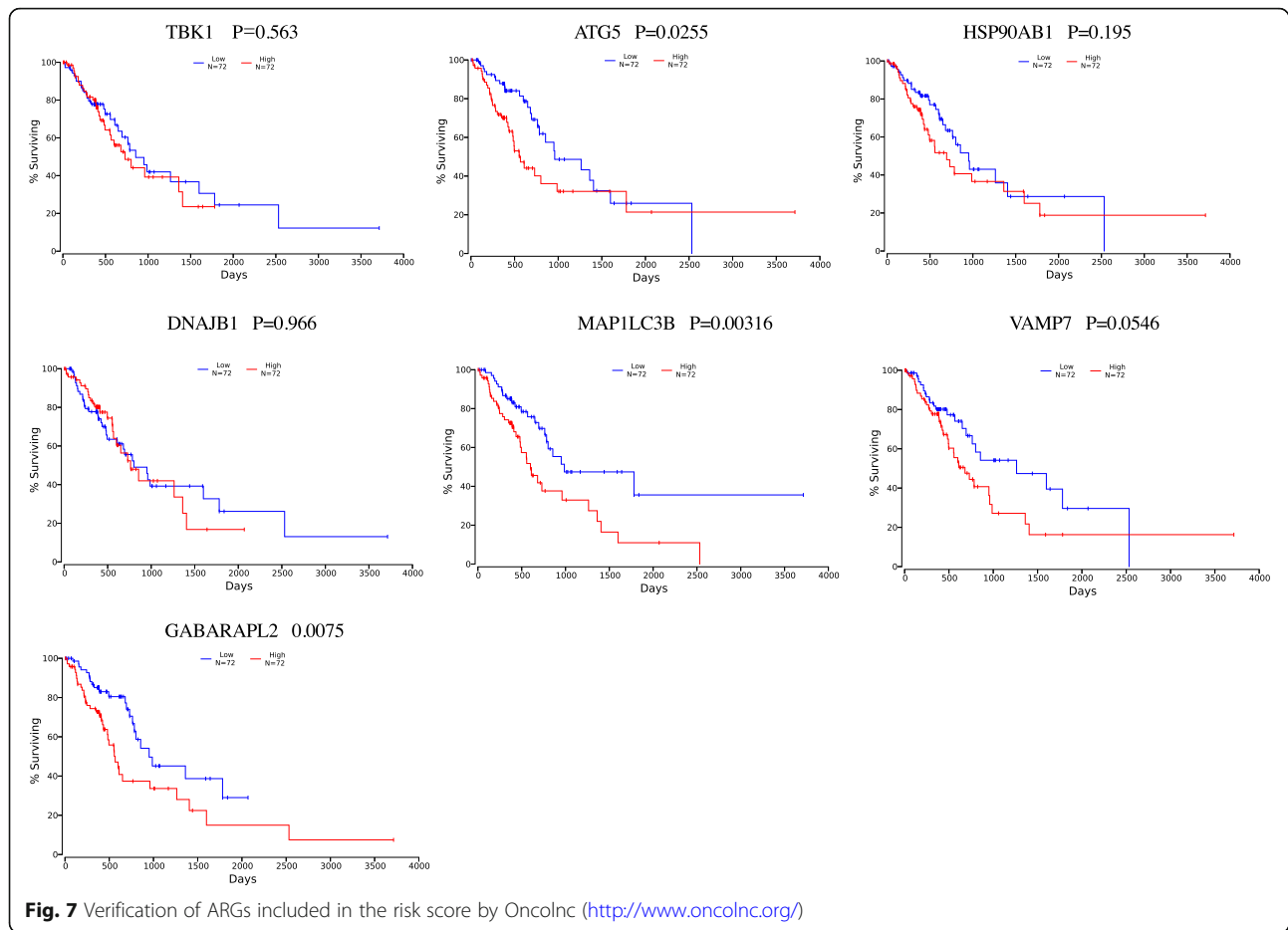
Firstly, our study verified the different expression of ARGs between esophageal carcinoma and normal tissues. Therefore, it may be of significant to exploit a useful autophagy-related risk score for patients with esophageal carcinoma. According to our result, the risk score calculated by the DEARGs score was superior to other classical clinical indicators.

Among the studies related to esophageal carcinoma, Langer et al. [23] showed that autophagy was correlated with esophageal carcinoma treatment and



diagnosis. To treat esophageal carcinoma using targeting ARGs, several studies try to develop the useful treatments for esophageal carcinoma through enhancing or inhibiting autophagy. In the study conducted by Huang, et al. [29], the results showed that Pristimerin reduced the growth of esophageal carcinoma. Moreover, previous studies also indicate that ginsenoside Rk3 [30] and Sinoporphyrin sodium

(DVIDMs)-Photodynamic therapy (PDT) [31], which exert their functions by targeting autophagy, inhibit the survival of esophageal carcinoma cells. Furthermore, other studies also illustrate that the treatment targeting autophagy contributes to enhancing the anti-tumor effect [32–34], which functions based on the chemotherapy agents (cisplatin [33], 5-fluorouracil (5-FU) [34]).



Our results in this study showed that several genes served as the risk factors for patient prognosis. Of them, ATG5 and TBK1 had attracted our great interests. For ATG5, Cheng et al. [33] demonstrated in the esophageal carcinoma study that ATG5 was involved in autophagy activation. Additionally, Zheng et al. [35] suggested that ATG5 inhibition contributed to treatment for esophageal carcinoma patients. Furthermore, autophagy abolition through the ATG5/7 re-sensitized EC109/CDDP knockdown or the use of pharmacological inhibitors is greatly significant [36] not only in the esophageal, but also in gastric [37], colorectal [38, 39], bladder [40], ovarian [41], and prostate cancers [42]. With regard to TBK1, it has been proven that TBK1 takes part in modulating cell growth and autophagy [43]. Moreover, Sarraf et al. [44] also indicated that TBK1 exerted an important role in mitophagy.

Conclusions

In conclusion, the major ARGs are taken to develop a novel scoring system in this study, which accurately predict the clinical outcomes for esophageal carcinoma patients. The included ARGs are confirmed using the

online dataset oncolnc. Therefore, our results show that ARGs can be recognized as the therapeutic targets and prognostic biomarkers for esophageal cancer. Nonetheless, our findings should be further investigated in the future.

Abbreviations

ARGs: Autophagy-related genes; OS: Overall survival; ROC: Receiver operating characteristic; AUC: Area under curve; TBK1: TANK-binding kinase 1; ATG5: Autophagy protein 5; HSP90AB1: Heat shock protein 90 kDa alpha, class B member 1; VAMP7: Vesicle-Associated Membrane Protein 7; DNAJB1: DnaJ homolog subfamily B member 1; GABARAPL2: Golgi-associated ATPase enhancer of 16 kDa; MAP2K7: Mitogen-activated protein kinase kinase 7; PET-CT: Positron Emission Tomography-Computed Tomography; HER2: Human Epidermal Growth Factor Receptor 2; PD-L1: Programmed Death 1; TCGA: The Cancer Genome Atlas; PCA: Principal component analysis; GO: Gene Ontology

Acknowledgements

Not Applicable.

Authors' contributions

HL and SLC designed the research protocol, analyzed data and revised the manuscript. CXC and SLC searched and analyzed the data. HJC and XCH wrote the manuscript and participated in analyzing data. JJW and TMW participated in searching the data. All authors have read and approved the manuscript.

Funding

Not applicable.

Availability of data and materials

Each dataset used in this study was searched based on the published literature, freely accessible from related authors upon request.

Ethics approval and consent to participate

All data were searched freely from Public Dataset based on the published literature. No permission was required. The following are the links of the related Dataset: Human autophagy database (<http://www.autophagy.lu/>), The Cancer Genome Atlas (<https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga>), OncoPrint (<http://www.oncoprint.org/>), Gene Ontology (<http://geneontology.org/>).

Consent for publication

Not applicable.

Competing interests

All authors declare no competing interest.

Author details

¹Department of Intensive Care Unit, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng Dong Road, Guangzhou 510060, People's Republic of China. ²Guangzhou Institute of Respiratory Diseases, State Key Laboratory of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. ³Department of hematology, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China. ⁴Department of VIP Inpatient, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China. ⁵Department of Tuberculosis, Fuzhou Pulmonary Hospital of Fujian, Fuzhou, China. ⁶School of Public Health, Sun Yat-sen University, Guangzhou, China.

Received: 10 December 2019 Accepted: 17 August 2020

Published online: 24 August 2020

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
- Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol Biomark Prev*. 2016;25(1):16–27.
- Zhao JK, Wu M, Kim CH, Jin ZY, Zhou JY, Han RQ, Yang J, Zhang XF, Wang XS, Liu AM, et al. Jiangsu four cancers study: a large case-control study of lung, liver, stomach, and esophageal cancers in Jiangsu Province, China. *Eur J Cancer Prev*. 2017;26(4):357–64.
- Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst*. 2003;95(18):1404–13.
- Chen CX, Bai L, Liu ZG, Zhou K, Lu WW, Zhao QY. Finding esophageal cancer: could initial blood cell counts tell us? *Int J Clin Exp Med*. 2019;12(6):7820–6.
- Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol*. 2013;24(3):609–17.
- Smith JW, Moreira J, Abood G, Aranha GV, Nagda S, Wagner RH, Shoup M. The influence of (18) fluorodeoxyglucose positron emission tomography on the management of gastroesophageal junction carcinoma. *Am J Surg*. 2009;197(3):308–12.
- Dreilich M, Wanders A, Brattstrom D, Bergstrom S, Hesselius P, Wagenius G, Bergqvist M. HER-2 overexpression (3+) in patients with squamous cell esophageal carcinoma correlates with poorer survival. *Dis Esophagus*. 2006;19(4):224–31.
- Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* (New York, NY). 2017;357(6349):409–13.
- Shitara K, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, Fornaro L, Olesinski T, Caglevic C, Chung HC, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* (London, England). 2018;392(10142):123–33.
- Chen CX, Ke HX, Shen XT, Yin M, Zhao QY. Risk factors of postoperative infection after McKeown esophagogastrectomy. *Int J Clin Exp Med*. 2018;11(5):5019–25.
- Chen C, Wen T, Zhao Q. The change of laboratory tests could be predictive factors for infection after McKeown Esophagogastrectomy. *Biomed Res Int*. 2019;2019:9718705.
- Dikic I, Johansen T, Kirkin V. Selective autophagy in cancer development and therapy. *Cancer Res*. 2010;70(9):3431–4.
- Macintosh RL, Ryan KM. Autophagy in tumour cell death. *Semin Cancer Biol*. 2013;23(5):344–51.
- Karsli-Uzunbas G, Guo JY, Price S, Teng X, Laddha SV, Khor S, Kalaany NY, Jacks T, Chan CS, Rabinowitz JD, et al. Autophagy is required for glucose homeostasis and lung tumor maintenance. *Cancer Discov*. 2014;4(8):914–27.
- Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, Rosen J, Eskelinen EL, Mizushima N, Ohsumi Y, et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J Clin Invest*. 2003;112(12):1809–20.
- Rao S, Tortola L, Perlot T, Wirsberger G, Novatchkova M, Nitsch R, Sykacek P, Frank L, Schramek D, Komnenovic V, et al. A dual role for autophagy in a murine model of lung cancer. *Nat Commun*. 2014;5:3056.
- Amaravadi R, Kimmelman AC, White E. Recent insights into the function of autophagy in cancer. *Genes Dev*. 2016;30(17):1913–30.
- Levy JM, Thorburn A. Targeting autophagy during cancer therapy to improve clinical outcomes. *Pharmacol Ther*. 2011;131(1):130–41.
- Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. *Nat Rev Cancer*. 2017;17(9):528–42.
- Towers CG, Thorburn A. Therapeutic targeting of autophagy. *EBioMedicine*. 2016;14:15–23.
- Galluzzi L, Pietrocola F, Levine B, Kroemer G. Metabolic control of autophagy. *Cell*. 2014;159(6):1263–76.
- Langer R, Streutker CJ, Swanson PE. Autophagy and its current relevance to the diagnosis and clinical management of esophageal diseases. *Ann N Y Acad Sci*. 2016;1381(1):113–21.
- Siewert JR, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? *Semin Radiat Oncol*. 2007;17(1):38–44.
- Marino G, Niso-Santano M, Baehrecke EH, Kroemer G. Self-consumption: the interplay of autophagy and apoptosis. *Nat Rev Mol Cell Biol*. 2014;15(2):81–94.
- Mathew R, Karp CM, Beaudoin B, Vuong N, Chen G, Chen HY, Bray K, Reddy A, Bhanot G, Gelinas C, et al. Autophagy suppresses tumorigenesis through elimination of p62. *Cell*. 2009;137(6):1062–75.
- Lorin S, Hamai A, Mehrpour M, Codogno P. Autophagy regulation and its role in cancer. *Semin Cancer Biol*. 2013;23(5):361–79.
- Sui X, Chen R, Wang Z, Huang Z, Kong N, Zhang M, Han W, Lou F, Yang J, Zhang Q, et al. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. *Cell Death Dis*. 2013;4:e838.
- Huang P, Sun LY, Zhang YQ. A hopeful natural product, Pristimerin, induces apoptosis, cell cycle arrest, and autophagy in esophageal Cancer cells. *Anal Cell Pathol (Amst)*. 2019;2019:6127169.
- Liu H, Zhao J, Fu R, Zhu C, Fan D. The ginsenoside Rk3 exerts anti-esophageal cancer activity in vitro and in vivo by mediating apoptosis and autophagy through regulation of the PI3K/Akt/mTOR pathway. *PLoS One*. 2019;14(5):e0216759.
- Shi Y, Zhang B, Feng X, Qu F, Wang S, Wu L, Wang X, Liu Q, Wang P, Zhang K. Apoptosis and autophagy induced by DVDMS-PDT on human esophageal cancer Eca-109 cells. *Photodiagn Photodyn Ther*. 2018;24:198–205.
- Falvey CM, O'Donovan TR, El-Mashed S, Nyhan MJ, O'Reilly S, McKenna SL. UBE2L6/UBCH8 and ISG15 attenuate autophagy in esophageal cancer cells. *Oncotarget*. 2017;8(14):23479–91.
- Cheng CY, Liu JC, Wang JJ, Li YH, Pan J, Zhang YR. Autophagy inhibition increased the anti-tumor effect of cisplatin on drug-resistant esophageal cancer cells. *J Biol Regul Homeost Agents*. 2017;31(3):645–52.
- Feng Y, Gao Y, Wang D, Xu Z, Sun W, Ren P. Autophagy inhibitor (LY294002) and 5-fluorouracil (5-FU) combination-based Nanoliposome for

- enhanced efficacy against esophageal squamous cell carcinoma. *Nanoscale Res Lett.* 2018;13(1):325.
35. Zheng K, Li Y, Wang S, Wang X, Liao C, Hu X, Fan L, Kang Q, Zeng Y, Wu X, et al. Inhibition of autophagosome-lysosome fusion by ginsenoside Ro via the ESR2-NCF1-ROS pathway sensitizes esophageal cancer cells to 5-fluorouracil-induced cell death via the CHEK1-mediated DNA damage checkpoint. *Autophagy.* 2016;12(9):1593–613.
 36. Yu L, Gu C, Zhong D, Shi L, Kong Y, Zhou Z, Liu S. Induction of autophagy counteracts the anticancer effect of cisplatin in human esophageal cancer cells with acquired drug resistance. *Cancer Lett.* 2014;355(1):34–45.
 37. Pei G, Luo M, Ni X, Wu J, Wang S, Ma Y, Yu J. Autophagy facilitates Metadherin-induced chemotherapy resistance through the AMPK/ATG5 pathway in gastric Cancer. *Cell Physiol Biochem.* 2018;46(2):847–59.
 38. Chen MC, Lin YC, Liao YH, Liou JP, Chen CH. MPTOG612, a Novel HDAC6 Inhibitor, Induces Apoptosis and Suppresses IFN-gamma-Induced Programmed Death-Ligand 1 in Human Colorectal Carcinoma Cells. *Cancers.* 2019;11(10). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6826904/>.
 39. Che J, Wang W, Huang Y, Zhang L, Zhao J, Zhang P, Yuan X. miR-20a inhibits hypoxia-induced autophagy by targeting ATG5/FIP200 in colorectal cancer. *Mol Carcinog.* 2019;58(7):1234–47.
 40. Quan Y, Lei H, Wahafu W, Liu Y, Ping H, Zhang X. Inhibition of autophagy enhances the anticancer effect of enzalutamide on bladder cancer. *Biomed Pharmacother.* 2019;120:109490.
 41. Luan W, Pang Y, Li R, Wei X, Jiao X, Shi J, Yu J, Mao H, Liu P. Akt/mTOR-mediated autophagy confers resistance to BET inhibitor JQ1 in ovarian Cancer. *Onco Targets Ther.* 2019;12:8063–74.
 42. Zhang N, Li Z, Bai F, Zhang S. PAX5-induced upregulation of IDH1-AS1 promotes tumor growth in prostate cancer by regulating ATG5-mediated autophagy. *Cell Death Dis.* 2019;10(10):734.
 43. Antonia RJ, Castillo J, Herring LE, Serafin DS, Liu P, Graves LM, Baldwin AS, Hagan RS. TBK1 limits mTORC1 by promoting phosphorylation of raptor Ser877. *Sci Rep.* 2019;9(1):13470.
 44. Sarraf SA, Sideris DP, Giagtzoglou N, Ni L, Kankel MW, Sen A, Bochicchio LE, Huang CH, Nussenzweig SC, Worley SH, et al. PINK1/Parkin Influences Cell Cycle by Sequestering TBK1 at Damaged Mitochondria, Inhibiting Mitosis. *Cell Rep.* 2019;29(1):225–35 e225.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

