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MINIREVIEWS

Oncologic impact of colonic stents for obstructive left-sided colon cancer

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Abstract

Colonic stenting has had a significant positive impact on the management of obstructive left-sided colon cancer (OLCC) in terms of both palliative treatment and bridge-to-surgery (BTS). Notably, many studies have convincingly demonstrated the effectiveness of stenting as a BTS, resulting in improvements in short-term outcomes and quality of life, safety, and efficacy in subsequent curative surgery, and increased cost-effectiveness, whereas the safety of chemotherapy after stenting and the long-term outcomes of stenting as a BTS are controversial. Several studies have suggested an increased risk of perforation in patients receiving bevacizumab chemotherapy after colonic stenting. In addition, several pathological analyses have suggested a negative oncological impact of colonic stenting. In contrast, many recent studies have demonstrated that colonic stenting for OLCC does not negatively impact the safety of chemotherapy or long-term oncological outcomes. The updated version of the European Society of Gastrointestinal Endoscopy guidelines released in 2020 included colonic stenting as a BTS for OLCC as a recommended treatment. It should be noted that the experience of endoscopists is involved in determining technical and clinical success rates and possibly oncological outcomes. This review discusses the positive and negative impacts of colonic stenting on OLCC treatment, particularly in terms of oncology.

Key Words: Colonic stents; Obstructive left-sided colon cancer; Bridge to surgery; Chemotherapy; Long-term outcomes; European Society of Gastrointestinal Endoscopy guidelines

Core Tip: Colonic stenting has been widely used in the management of obstructive left-sided colon cancer, and its effectiveness has been convincingly demonstrated. However, some controversies remain, including the safety of chemotherapy after stenting and the long-term outcomes of stenting as a bridge to surgery (BTS). Nevertheless, many recent studies have demonstrated that colonic stenting exerts no negative impact on long-term oncological outcomes, and this technique is recommended as a BTS in the European Society of Gastrointestinal Endoscopy guidelines. Herein, we review and discuss the positive and negative effects of colonic stenting in colon cancer treatment.

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INTRODUCTION

Colorectal cancer remains one of the most common malignant diseases worldwide. Among all patients with colorectal cancer, approximately 10% present with large bowel obstruction[1]. The most common location for obstructive colon cancer (OCC) is the sigmoid colon, and more than 75% of OCC are located on the left side, i.e., distal to the splenic flexure[2].

Emergency surgery (ES) has traditionally been the mainstay of OCC management. There are several options for ES procedures to treat obstructive left-sided colon cancer (OLCC); however, a stoma is often needed in any case. Patients with clinically severe instability or in whom resection is not possible should be treated with diverting loop colostomy[3]. Hartmann's procedure, that is, resection of the diseased colon or rectum with end colostomy, has been widely performed for resectable OLCC[4]. Resection with primary anastomosis could be considered an option during ES for resectable cases; due to the risk of anastomotic leakage, a temporary diverting stoma can be created simultaneously in many cases. However, the reversal rate of stomas is relatively low when created under these conditions. Öistämö *et al*[5] retrospectively analyzed acute cases of OLCC and demonstrated that 35% of stomas created with the intention of being temporary were never reversed. Stomas can have a negative impact on the patient's body image and quality of life (QOL). Additionally, diverting stoma formation in colorectal resection for OCC is related to increased postoperative complications, failure to wean off the ventilator, and longer hospital stays[6].

Colonic stenting is a powerful modality for intestinal decompression to resolve problems associated with ES. In addition, recent advances in stent technology have profoundly impacted OLCC management. Herein, we review the current state of colonic stenting and discuss its impact on colorectal cancer treatment, particularly focusing on its relationship with oncology.

HISTORY AND INDICATION

Palliative purpose and bridge to surgery

There are two main purposes of colonic stenting for OCC: palliative treatment and bridge to surgery (BTS). In this context, palliative treatment involves stenting applied to patients with an unresectable lesion, while BTS comprises preoperative stenting for intestinal decompression until the condition suitable for curative surgery is improved[7]. In comparison, colonic stenting for palliative purposes has a long history of use. Colonic stents were first reported by Dohmoto *et al*[8] in 1991. This study reported using stents for palliative treatment of OCC. Since then, many studies have elucidated the usefulness of colonic stents for palliative treatment in patients requiring intestinal decompression. In addition, the effectiveness of short-term outcomes of stent placement for unresectable colorectal cancer has been widely recognized, at least in the late 20th century[9,10].

Recently, self-expandable metallic stents (SEMS) as BTS have been widely used. Relief from obstruction with BTS enables restoration of dilated intestinal conditions prior to surgery, decreases mortality and morbidity, avoids stoma, and improves the quality of life[11]. Importantly, colonic stenting as a BTS should be performed under strict indications compared with stenting for palliative treatment, as BTS ultimately aims at a radical cure and requires long-term safety.

Left-sided vs right-sided colon

Stents can be placed not only in the left-sided colon but also in the right-sided colon. Although some reports have suggested that obstructive right-sided colonic cancer is also a good indication of SEMS, the effectiveness of SEMS for right-sided colonic obstruction has been less reported than that for left-sided

colonic obstruction[9]. Morita *et al*[12] analyzed the advantages of SEMS as a BTS over primary surgery in a retrospective, multicenter cohort study. When patients with left-sided colon cancer were compared, the rates of primary resection with anastomosis and stoma-free surgery were significantly higher in the SEMS group, whereas when patients with right-sided colon cancer were compared, no significant difference in the rates was observed between the SEMS and primary surgery groups. In addition, several disadvantages of SEMS placement in the right-sided colon have been pointed out, including a lower technical success rate and longer procedure time[13-15]. The authors of the European Society of Gastrointestinal Endoscopy (ESGE) guidelines also suggested the difficulty of stenting in the colon proximal to the splenic flexure and emphasized that SEMS recommendations should be applied to left-sided colon cancer[16].

TECHNICAL AND CLINICAL SUCCESS RATES

Recent studies have reported high technical and clinical success rates of SEMS placement for OCC. In a meta-analysis published in 2021, Neo *et al*[17] examined the technical and clinical success rates of SEMS for colorectal obstruction. In this study, technical success was defined as successful placement and deployment of the stent, and clinical success was defined as colonic decompression within 96 h after the stent was successfully placed. The technical and clinical success rates of SEMS were 92% in 1550 patients [95% confidence interval (CI): 0.88-0.95] and 82% in 1105 patients (95%CI: 0.77-0.87), respectively. In another meta-analysis published in 2021, the success rates were compared between SEMS and transanal decompression tubes (TDT). The overall success rates of SEMS and TDT were 92.1% and 71.9%, respectively, and both the technical and clinical success rates of SEMS were significantly better than those of TDT[18].

Some reports have suggested that technical and clinical success rates depend on the operators' experience, with experience of at least 20-30 cases required to ensure safety and effectiveness[15,19]. In addition, Boyle *et al*[20] identified short strictures and wide angulations distal to the stricture as factors indicating successful stenting in colonic obstruction. A post hoc analysis of a multicenter clinical trial in Japan identified several factors related to the difficulty of SEMS placement, including peritoneal carcinomatosis or expansive strictures[13].

The Japan Colonic Stent Safe Procedure Research Group proposed a scoring system for the clinical features of colorectal obstruction according to the patient's oral intake status, termed the ColoRectal Obstruction Scoring System (CROSS). This system scores patients on a scale of 0-4 as follows: 0, requiring continuous decompression; 1, no oral intake; 2, liquid or enteral nutrition; 3, oral intake of soft solids, low-residue diet, or full diet with symptoms of stricture; and 4, oral intake of soft solids, low-residue diet, or full diet without symptoms of stricture[21]. The above-mentioned post-hoc analysis suggested that CROSS 0 before stenting was one of the factors related to the difficulty of SEMS placement[13]. In contrast, another post-hoc analysis of multicenter clinical trials showed that SEMS as BTS in CROSS 0 patients showed comparable technical and clinical success rates, safety, and short-term outcomes to those in CROSS 1 and 2 patients[22]. Thus, it is inconclusive whether CROSS 0 before SEMS placement affects the technical and clinical success rates of SEMS.

COMPLICATIONS

Perforation

Perforation is one of the most common and critical complications of SEMS placement. A recent meta-analysis demonstrated that the overall perforation rate of colonic stenting for OLCC is 5%[17]. In addition, several studies have reported the outcomes of patients with stent-related perforations or factors related to stent-related perforations.

According to the meta-analysis mentioned above, when the studies were compared between perforation rates > 8% and ≤ 8%, the perforation rate > 8% group showed poorer technical success rates, although the 5-year overall and disease-free survival rates were not significantly different[17]. In a Dutch randomized clinical trial, the SEMS in the BTS group tended to have a lower 4-year disease-free survival rate than that in the ES group. In addition, the subgroup with stent-related perforation had a significantly poorer disease-free survival than the ES group, which suggested that stent-related perforation exacerbated oncological outcomes. However, it should be noted that in this trial, the number of patients was small, and the stent-related perforation rate was high (approximately 23%)[23]. Furthermore, it should also be noted that ES had better postoperative outcomes than BTS by stent because of the lower success rate of stent placement reported prior to 2014.

Datye *et al*[24] aggregated articles on perforation after SEMS placement for OCC until 2008 and analyzed data such as causes and mortality. The overall perforation rate was 4.9%, and concomitant chemotherapy, steroids, and radiotherapy were identified as risk factors for perforation; however, no significant difference was observed in the perforation rate between palliative treatment and BTS. The

authors also emphasized a high mortality rate of perforation cases (16%); however, the data did not necessarily show a negative impact of SEMS itself, considering the low overall perforation-related mortality rate (0.8%) and high mortality rate of ES (15%-20%).

van Halsema *et al*[25] pointed to the stent type as a risk factor for perforation. The authors defined stent types with high (< 10%) (WallFlex, Comvi, and Niti-S D-type) and low (< 5%) (Hanarostent and Niti-S covered) perforation rates. In fact, the perforation rates of certain stent types, especially the WallFlex stent, vary across reports. For example, Meisner *et al*[26] demonstrated that the overall perforation rate of WallFlex stent placement for OCC was 5.1% in 255 cases in prospective and multicenter studies. In a prospective multicenter study using WallFlex stent in Japan, the perforation rate was reported to be 1.6%[27]. van Halsema *et al*[25] reported a relatively high occurrence of delayed perforation after WallFlex stent placement and considered that the short follow-up period may have reduced the overall perforation rate of the stent.

Migration and re-obstruction

According to a systematic review, the rate of stent migration is approximately 10% (interquartile range 3%-22%). In this report, laser pretreatment and chemotherapy were identified as factors that promote stent migration[28]. Because the high risk of perforation and migration has been mentioned, laser or balloon dilation prior to stent placement is not recommended[28-30]. The overall re-obstruction rate was reported to be 10% (interquartile range 0%-15%), and when the cases were limited to palliative treatment, the re-obstruction rate was 16% (interquartile range 0%-23%)[28].

Safety of chemotherapy

The negative impact of SEMS on colorectal cancer management has been demonstrated in several respects, including chemotherapy after SEMS placement, which raised the concern that chemotherapy after SEMS placement may increase the risk of perforation. In theory, chemotherapy destroys proliferating cancer cells in the colonic wall; therefore, it can provoke stent-related perforation[25]. Although the safety of chemotherapy after SEMS placement remains to be fully elucidated[31], several recent studies have suggested an answer.

In a retrospective study that reviewed patients who underwent SEMS placement, the perforation rates were 13% in patients receiving no chemotherapy, 6% in patients receiving chemotherapy without bevacizumab, and 20% in patients receiving chemotherapy with bevacizumab[32]. Another retrospective study also suggested that subsequent bevacizumab therapy increased the risk of complications after SEMS insertion, and the perforation risk increased nearly threefold[33]. A meta-analysis of studies between 2005 and 2011 further revealed that the perforation rate in patients receiving bevacizumab-based chemotherapy was significantly higher than that in patients receiving no chemotherapy, whereas the perforation rate in patients receiving non-bevacizumab-based chemotherapy was significantly lower than that in patients who received no chemotherapy[25].

Some reports have demonstrated that chemotherapy does not affect the SEMS complications. However, a recent retrospective analysis indicated that chemotherapy before SEMS increased the risk of stent-related complications, whereas chemotherapy after SEMS had no impact on complications[34]. In a single-center retrospective study, Lee *et al*[35] compared the adverse events of SEMS as a palliative treatment for OCC between patients receiving bevacizumab therapy and those not receiving bevacizumab therapy. In this study, the perforation rate in the bevacizumab group was only 1%, which was equivalent to that of the non-bevacizumab group (3%). The authors considered that the low perforation rate might be related to the many years of experience of endoscopists. Additionally, one retrospective study showed the effectiveness and safety of SEMS before neoadjuvant chemotherapy and curative surgery, although the sample size was small. This study suggested the relatively low toxicity and high tolerability of neoadjuvant chemotherapy with two cycles of CAPOX or three cycles of mFOLFOX6 after SEMS. The resected specimens were also analyzed, suggesting a low risk of perineural invasion[36].

POSITIONING IN GUIDELINES

The degree of recommendation for SEMS as palliative management or BTS for OLCC has been described in many international guidelines, and the description seems to change with time. Herein, recent changes in the positioning of SEMS in the guidelines and the impact of changes in the description of SEMS are discussed below.

Webster *et al*[37] reviewed 19 international guidelines for the management of OLCC between 2010 and 2018. Stenting for palliative management was recommended in most guidelines, whereas opinions regarding the recommendation of emergency stenting as a BTS were divided. Eight guidelines recommended ES, two from the United States recommended emergency stenting as BTS, and nine suggested either ES or stenting as BTS could be selected. Guidelines from countries other than the United States did not actively recommend SEMS as a BTS until recently.

However, the description of the recommendations in the ESGE guidelines has recently changed. In the ESGE guidelines published in 2014, SEMS as BTS for OLCC was not recommended because of the risk of stent-related complications, particularly perforation[38]. In recent years, many studies have revealed the long-term safety of SEMS as a BTS; therefore, the description of the ESGE guidelines regarding the use of SEMS for OCC was updated in 2020, and SEMS as a BTS for OLCC has become a recommended treatment[16].

The impact of these updated recommendations in the guidelines has also been reported. The national colorectal cancer guidelines were updated in the Netherlands in 2014, and SEMS as a BTS for OLCC is clearly recommended. Consequently, the application rates of ES and SEMS for OLCC were reversed, and some changes occurred after 2014 in the Netherlands: the proportion of laparoscopic surgery increased, and the permanent stoma rate and total hospital stay decreased[39].

Despite the major impact of the guidelines on treatment, it should be noted that concerns regarding the quality of the guidelines have also been reported. Gavriilidis *et al*[40] used the Appraisal of Guidelines for Research and Evaluation II instrument to evaluate the quality of the 14 current guidelines describing the management of OLCC. The authors pointed out a poor applicability score in many guidelines and concerns regarding variations in guideline quality. Further research may trigger more changes to the description of guidelines and improve their quality.

SHORT-TERM AND LONG-TERM OUTCOMES

Short-term outcomes

Traditionally, in many cases of OCC, emergency decompression surgery was performed without adequate evaluation of preoperative staging and comorbidity. As a result, the risk of morbidity and mortality was unavoidably involved. SEMS as a BTS is considered a valid option for these cases as it can offer plenty of time to evaluate preoperative problems and improve the medical condition of patients [9]. Based on this perspective, it is not surprising that SEMS as a BTS has been reported to be advantageous in terms of short-term outcomes compared to ES. In a meta-analysis of randomized controlled trials comparing SEMS as BTS and ES for OLCC, the need for stoma creation, the incidence of postoperative complications, and the occurrence of wound infection were significantly reduced in the SEMS group[41].

TDT is another option for BTS of OCC; however, TDT has more disadvantages than SEMS: Slow decompression, bad odor, complicated management, difficult oral intake, and poor QOL[42]. Furthermore, several meta-analyses have compared the short-term outcomes between SEMS and TDT, and TDT was found to have poorer short-term outcomes. TDT showed lower clinical and technical success rates, solid food intake, and temporal discharge in a subsequent operation; TDT increased blood loss, prolonged operative time, and enhanced stoma rates[18,43]. In the context of these circumstances, the ESGE guidelines updated in 2020 do not recommend TDT placement over SEMS placement[16].

Negative reports on long-term outcomes

The advantages of SEMS as a BTS in short-term outcomes have been convincingly demonstrated, whereas the long-term outcomes of SEMS as a BTS have been controversial. In other words, the oncological safety of SEMS as a BTS remains unclear. However, high-quality research on the long-term outcomes of SEMS as a BTS has been increasing in recent years. Thus far, several studies have suggested the negative oncological impact of SEMS placement (Table 1). In a meta-analysis of randomized control trials, although no significant differences were observed in 3-year disease-free survival or overall survival between the SEMS as BTS group and ES group, the risk of systemic recurrence was significantly higher in the SEMS group than in the ES group[44]. Katsuki *et al*[45] analyzed a nationwide inpatient database in Japan and conducted a retrospective cohort study using propensity score-matching. The authors compared the long-term outcomes of patients with OLCC between SEMS as BTS and ES and demonstrated that the SEMS group showed significantly worse overall survival than the ES group. Gorissen *et al*[46] analyzed OLCC patients aged 75 years and younger from a prospective cohort study. In this study, the local recurrence rate in the SEMS group was significantly higher than that in the ES group, and the authors concluded that SEMS was associated with an increase in local recurrence, particularly in younger patients. Uehara *et al*[47] retrospectively evaluated the oncological outcomes of SEMS in patients with stage II or III OCC. The authors reported a higher distant metastatic recurrence rate in the SEMS group than in the ES group. Mege *et al*[48] examined the overall and disease-free survival of patients who underwent SEMS placement or creation of decompression stoma as a BTS for OLCC in a multicenter retrospective study. The authors demonstrated a significantly lower overall survival rate in the SEMS group, which may be related to an increase in worse pathological findings, such as tumor perforation. Sabbagh *et al*[49] reported significantly lower overall survival and significantly higher cancer-specific mortality in the SEMS group than in the ES group.

Table 1 Recent reports on long-term outcomes of colonic stenting as a bridge to surgery for obstructive left-sided colon cancer

Ref.	Publication year	Study type	Number of stent placements	Disease-free survival	Overall survival	Overall recurrence	Systemic recurrence	Local recurrence
Foo *et al* [44]	2019	Meta-analysis	222	NS	NS	SEMS > ES	SEMS > ES	NS
Katsuki *et al*[45]	2021	Multi-center retrospective study	498	NA	SEMS < ES	NA	NA	NA
Gorissen *et al*[46]	2013	Single-center prospective study	62	NS	NS	NS	NS	SEMS > ES in patients aged ≤ 75
Uehara *et al* [47]	2022	Single-center retrospective study	43	NS	NS	NA	SEMS > ES	NS
Mege *et al* [48]	2019	Multi-center retrospective study	191	NS	SEMS < DS	NA	NA	NA
Sabbagh *et al*[49]	2013	Multi-center retrospective study	48	NS	SEMS < ES	NS	NA	NA
Cirocchi *et al*[56]	2021	Meta-analysis	102-148	NS	NS	NS	NS	NS
Arezzo *et al* [57]	2017	Multi-center RCT	56	NS	NS	NS	NS	NS
Amelung *et al*[58]	2019	Multi-center retrospective study	222	NS	NS	NS	NS	NS
Veld *et al* [59]	2020	Multi-center retrospective study	121	NS	NS	NS	NS	NS
Endo *et al* [60]	2021	Multi-center retrospective study	113	TDT > ES (SEMS *vs* ES: NS)	NA	TDT > ES (SEMS *vs* ES: NS)	NS	NS
Kim *et al* [61]	2022	Single-center retrospective	98	NS	NS	NA	NA	NA

RCT: Randomized clinical trial; SEMS: Self-expandable metallic stent; ES: Emergency surgery; DS: Decompression stoma; TDT: Transanal decompression tube; NS: Not significant; NA: Not available.

Negative reports in pathological studies

As mentioned above, the potential negative impact of SEMS on oncological outcomes has also been suggested through histopathological examinations. Sabbagh *et al*[50] conducted a pathological analysis and revealed that tumor and peritumor ulceration, perineural invasion, and lymph node invasion were seen more frequently in resected specimens after SEMS placement than in cases of surgery only. These pathological features are associated with poor prognosis. Other authors have also reported negative factors for SEMS placement from a pathological viewpoint. Zhang *et al*[51] analyzed the histopathological findings of specimens resected after SEMS or TDT for OLCC. The authors reported that vascular invasions, wound abscesses, and ulcer formation was more frequently observed in the SEMS group than in the TDT group.

Some reports have also indirectly suggested the negative impact of SEMS on colorectal cancer treatment through analysis of the peripheral blood of patients. Maruthachalam *et al*[52] reported that circulating cytokeratin 20 mRNA levels after stent placement for left-sided colon cancer was significantly higher than before stenting, suggesting the possibility of tumor manipulation by inserting a guidewire or dilating and deploying the stent. Yamashita *et al*[53] showed an increase in viable circulating tumor cells after SEMS placement for OCC, which suggested that SEMS placement and expansion could allow the release of colorectal cancer cells into circulation. Recent technological developments in genome sequencing and molecular diagnosis have allowed the measurement of circulating tumor DNA (ctDNA), which is released from tumor cells undergoing apoptosis or necrosis into the systemic circulation[54]. The use of ctDNA has been extensively evaluated as a promising biomarker for the treatment of colorectal cancer. Takahashi *et al*[55] demonstrated that the plasma levels of ctDNA in patients with OCC increased after SEMS placement, although this increase was not

observed after TDT insertion. These findings indicate that SEMS placement may induce tumor cell dissemination. However, it remains unclear whether these changes in peripheral blood are related to the long-term oncological prognosis of patients.

Positive reports on long-term outcomes

As mentioned below, the oncological prognosis of SEMS as BTS is equivalent to that of ES and has been increasing in recent years (Table 1). In a meta-analysis of randomized controlled trials comparing SEMS as BTS and ES for OCC, SEMS showed the same mortality and significantly lower morbidity than ES. In addition, recurrence and survival outcomes were not significantly different between SEMS and ES[56]. Arezzo *et al*[57] demonstrated no significant differences in 3-year overall survival rates or progression-free survival rates observed between SEMS as a BTS and ES in a large multicenter randomized controlled trial. In addition, considering the significantly lower stoma rate in the SEMS group, the authors concluded that SEMS as a BTS was a viable approach for OCC. Amelung *et al*[58] retrospectively compared the long-term outcomes of patients with OLCC between SEMS as BTS and ES using propensity score matching, showing no significant differences in the 3-year disease-free survival rates, overall survival rates, or locoregional recurrence rates, whereas the SEMS group showed a lower permanent stoma risk. In a cohort study in the Netherlands, decompressing stoma and SEMS were compared to determine which has advantages as a BTS for OLCC. The study showed no significant differences in the 3-year locoregional recurrence rates, disease-free survival rates, or overall survival rates[59]. Endo *et al*[60] reported that the long-term oncologic outcome of SEMS as BTS for patients with OLCC was comparable to that of ES, whereas the long-term outcome of TDT was poorer than that of ES.

A recent Korean retrospective study examining the long-term outcomes of SEMS as BTS for OCC further found no significant difference in the 5-year overall survival and 5-year disease-free survival between the SEMS and ES groups. The authors emphasized the high technical and clinical success rates (99% and 92.9%, respectively) and a low perforation rate (1%) in the study, which could be due to the highly experienced endoscopist. Similarly, SEMS placement performed by experienced endoscopists may improve oncological outcomes[61]. Thus, endoscopist experience also seems to influence the long-term prognosis of patients. Amelung *et al*[62] performed a systematic review and meta-analysis of patients with OLCC to compare the long-term oncological outcomes after SEMS as a BTS with those after ES. The authors demonstrated that SEMS placement showed a significant survival benefit in more than 40 patients. The ESGE also recommends that an experienced endoscopist should perform or directly supervise stent placement[16].

CURATIVE SURGERY AFTER COLONIC STENTING

In cases of resectable OLCC, SEMS can facilitate the performance of minimally invasive one-stage surgery safely and effectively, which is one of the major benefits of SEMS as a BTS. Enomoto *et al*[63] compared laparoscopic and open surgery after SEMS insertion for OCC. Blood loss in the laparoscopic surgery group was less than that in the open surgery group, whereas the operative time was significantly shorter in the open surgery group.

The safety and efficacy of robot-assisted laparoscopic surgery after SEMS placement have also been reported recently[64]. Li *et al*[65] analyzed 79 cases where SEMS placement was performed for OCC in the largest single center in Singapore from 2013 to 2020. The authors showed that 14% of the patients underwent robot-assisted surgery for curative surgery. The progression and spread of minimally invasive surgery for colorectal cancer can strengthen the benefits of SEMS as BTS.

No consensus has yet been reached regarding the proper waiting period between SEMS insertion and curative surgery. Sato *et al*[66] retrospectively analyzed the long-term oncological outcomes of patients with OCC who underwent SEMS placement and curative surgery. The authors found that relapse-free survival was significantly shortened when the interval between stenting and curative surgery was longer than 16 d. Another retrospective study examining long-term outcomes after SEMS as a BTS for OCC further demonstrated that the risk of recurrence is associated with a long interval (longer than 18 d) between stenting and curative surgery[67]. In a nationwide cohort study in the Netherlands, patients with OLCC receiving SEMS as a BTS were divided into three groups according to the interval between stenting and surgery, as follows: 5-10 d group, 11-17 d group, and > 17 d. No significant differences were observed in 3-year disease-free survival or overall survival between the groups, although short-term outcomes were generally better in the 11-17 d group than in the 5-10 d and > 17 d groups[68]. In the ESGE guidelines published in 2014, the suggested time interval from colonic stenting as BTS to elective surgery was 5-10 d in patients with left-sided colon cancer; however, recent ESGE guidelines suggested a time interval of approximately 2 wk until resection[16,38]. In addition, the authors of the recent ESGE guidelines further described that the time interval should be determined considering the balance between stent-related adverse events and surgical outcomes because a short interval can reduce stent-related adverse events, whereas a long interval can improve surgical outcomes[16]. It should also be noted that ctDNA concentration was reported to increase over time following SEMS placement, which implies that a long interval may worsen the oncological outcome[55]. At any rate, as there is no

prospective comparative study on this matter[16], the optimal time interval between SEMS and curative surgery remains uncertain, and further research is required.

COST-EFFECTIVENESS

Many reports have shown that SEMS is cost-effective for both palliative intervention and BTS. Quinn *et al*[69] analyzed the costs and effectiveness in patients with unresectable or metastatic colorectal cancer who received SEMS or ES for acute colonic obstruction using decision tree analysis. The authors demonstrated that SEMS is a more cost-effective treatment for palliative intervention than ES. In a Japanese single-center retrospective study, short-term outcomes and total healthcare costs were compared between the SEMS, curative surgery, and ES groups. The study showed earlier oral intake, shorter total hospital stay, and lower total costs in the SEMS group than in the ES group, which suggested that SEMS as BTS was a more cost-effective treatment[70]. A Canadian decision analysis performed in 2006 elucidated the cost-effectiveness of SEMS as a BTS compared with the conventional surgical approach for acute OLCC[71].

Despite these studies, many clinicians may still regard SEMS for BTS as a treatment with lower cost-effectiveness. Suen *et al*[72] administered a questionnaire to Oceanian surgeons, surveying their intention to participate in randomized controlled trials on stent placement for OCC. Most surgeons gave a positive response to using stents for palliative treatment, whereas the majority of surgeons gave a negative response to using stents as BTS because they considered stenting as a BTS less cost-effective than ES.

CONCLUSION

Colonic stenting has had a positive impact on the management of OLCC, including facilitating the avoidance of stoma and reducing postoperative complications in the subsequent curative surgery, whereas a negative impact of colonic stenting on long-term oncologic outcomes seemed to have been emphasized until a decade ago. Many recent studies have demonstrated the long-term safety of colonic stenting for OLCC, which led to a change in the ESGE guidelines updated in 2020 as follows: SEMS as a BTS for OLCC is a recommended treatment. It should be noted that the experience of endoscopists is involved in determining the technical and clinical success rates and possibly the oncological outcomes. Uncertainty remains regarding SEMS placement for OLCC, including the long-term oncologic prognosis and safety of chemotherapy after SEMS; further investigation will be needed to clarify these points in the future.

FOOTNOTES

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REFERENCES

1 **Yeo HL**, Lee SW. Colorectal emergencies: review and controversies in the management of large bowel obstruction. *J*

Gastrointest Surg 2013; **17**: 2007-2012 [PMID: 24048614 DOI: 10.1007/s11605-013-2343-x]

2 **Frago R**, Ramirez E, Millan M, Kreisler E, del Valle E, Biondo S. Current management of acute malignant large bowel obstruction: a systematic review. *Am J Surg* 2014; **207**: 127-138 [PMID: 24124659 DOI: 10.1016/j.amjsurg.2013.07.027]

3 **Pisano M**, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, Agresta F, Allievi N, Bellanova G, Coccolini F, Coy C, Fugazzola P, Martinez CA, Montori G, Paolillo C, Penachim TJ, Pereira B, Reis T, Restivo A, Rezende-Neto J, Sartelli M, Valentino M, Abu-Zidan FM, Ashkenazi I, Bala M, Chiara O, De' Angelis N, Deidda S, De Simone B, Di Saverio S, Finotti E, Kenji I, Moore E, Wexner S, Biffl W, Coimbra R, Guttadauro A, Leppäniemi A, Maier R, Magnone S, Mefire AC, Peitzmann A, Sakakushev B, Sugrue M, Viale P, Weber D, Kashuk J, Fraga GP, Kluger I, Catena F, Ansaloni L. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg* 2018; **13**: 36 [PMID: 30123315 DOI: 10.1186/s13017-018-0192-3]

4 **Meyer F**, Marusch F, Koch A, Meyer L, Führer S, Köckerling F, Lippert H, Gastinger I; German Study Group "Colorectal Carcinoma (Primary Tumor)". Emergency operation in carcinomas of the left colon: value of Hartmann's procedure. *Tech Coloproctol* 2004; **8** Suppl 1: s226-s229 [PMID: 15655630 DOI: 10.1007/s10151-004-0164-3]

5 **Öistämö E**, Hjern F, Blomqvist L, Falkén Y, Pekkari K, Abraham-Nordling M. Emergency management with resection *vs* proximal stoma or stent treatment and planned resection in malignant left-sided colon obstruction. *World J Surg Oncol* 2016; **14**: 232 [PMID: 27577887 DOI: 10.1186/s12957-016-0994-2]

6 **Shwaartz C**, Fields AC, Prigoff JG, Aalberg JJ, Divino CM. Should patients With obstructing colorectal cancer have proximal diversion? *Am J Surg* 2017; **213**: 742-747 [PMID: 27742029 DOI: 10.1016/j.amjsurg.2016.08.005]

7 **Seo SY**, Kim SW. Endoscopic Management of Malignant Colonic Obstruction. *Clin Endosc* 2020; **53**: 9-17 [PMID: 31906606 DOI: 10.5946/ce.2019.051]

8 **Dohmoto M**. New method-endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. *Endoscopia Digestiva* 1991; **3**: 1507-1512

9 **Kim EJ**, Kim YJ. Stents for colorectal obstruction: Past, present, and future. *World J Gastroenterol* 2016; **22**: 842-852 [PMID: 26811630 DOI: 10.3748/wjg.v22.i2.842]

10 **Liberman H**, Adams DR, Blatchford GJ, Ternent CA, Christensen MA, Thorson AG. Clinical use of the self-expanding metallic stent in the management of colorectal cancer. *Am J Surg* 2000; **180**: 407-11; discussion 412 [PMID: 11182388 DOI: 10.1016/s0002-9610(00)00492-x]

11 **Lauro A**, Binetti M, Vaccari S, Cervellera M, Tonini V. Obstructing Left-Sided Colonic Cancer: Is Endoscopic Stenting a Bridge to Surgery or a Bridge to Nowhere? *Dig Dis Sci* 2020; **65**: 2789-2799 [PMID: 32583222 DOI: 10.1007/s10620-020-06403-2]

12 **Morita S**, Yamamoto K, Ogawa A, Naito A, Mizuno H, Yoshioka S, Matsumura T, Ohta K, Suzuki R, Matsuda C, Hata T, Nishimura J, Mizushima T, Doki Y, Mori M; Clinical Study Group of Osaka University (CSGO), Colorectal Group. Benefits of using a self-expandable metallic stent as a bridge to surgery for right- and left-sided obstructive colorectal cancers. *Surg Today* 2019; **49**: 32-37 [PMID: 30105529 DOI: 10.1007/s00595-018-1701-4]

13 **Kuwai T**, Yamaguchi T, Imagawa H, Yoshida S, Isayama H, Matsuzawa T, Yamada T, Saito S, Shimada M, Hirata N, Sasaki T, Koizumi K, Maetani I, Saida Y. Factors related to difficult self-expandable metallic stent placement for malignant colonic obstruction: A post-hoc analysis of a multicenter study across Japan. *Dig Endosc* 2019; **31**: 51-58 [PMID: 30113095 DOI: 10.1111/den.13260]

14 **Yoon JY**, Jung YS, Hong SP, Kim TI, Kim WH, Cheon JH. Clinical outcomes and risk factors for technical and clinical failures of self-expandable metal stent insertion for malignant colorectal obstruction. *Gastrointest Endosc* 2011; **74**: 858-868 [PMID: 21862005 DOI: 10.1016/j.gie.2011.05.044]

15 **Lee HJ**, Park SJ, Cheon JH, Kim TI, Kim WH, Hong SP. What is the necessity of endoscopist for successful endoscopic stenting in patients with malignant colorectal obstruction? *Int J Colorectal Dis* 2015; **30**: 119-125 [PMID: 25376335 DOI: 10.1007/s00384-014-2060-2]

16 **van Hooft JE**, Veld JV, Arnold D, Beets-Tan RGH, Everett S, Götz M, van Halsema EE, Hill J, Manes G, Meisner S, Rodrigues-Pinto E, Sabbagh C, Vandervoort J, Tanis PJ, Vanbiervliet G, Arezzo A. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2020. *Endoscopy* 2020; **52**: 389-407 [PMID: 32259849 DOI: 10.1055/a-1140-3017]

17 **Neo VSQ**, Jain SR, Yeo JW, Ng CH, Gan TRX, Tan E, Chong CS. Controversies of colonic stenting in obstructive left colorectal cancer: a critical analysis with meta-analysis and meta-regression. *Int J Colorectal Dis* 2021; **36**: 689-700 [PMID: 33495871 DOI: 10.1007/s00384-021-03834-9]

18 **Chen F**, Dong Q, Zhang F. Is self-expandable metallic stents superior to transanal decompression tubes for the treatment of malignant large-bowel obstruction: a meta-analysis. *Ann Palliat Med* 2021; **10**: 7378-7387 [PMID: 34263636 DOI: 10.21037/apm-20-2600]

19 **Williams D**, Law R, Pullyblank AM. Colorectal stenting in malignant large bowel obstruction: the learning curve. *Int J Surg Oncol* 2011; **2011**: 917848 [PMID: 22312531 DOI: 10.1155/2011/917848]

20 **Boyle DJ**, Thorn C, Saini A, Elton C, Atkin GK, Mitchell IC, Lotzof K, Marcus A, Mathur P. Predictive factors for successful colonic stenting in acute large-bowel obstruction: a 15-year cohort analysis. *Dis Colon Rectum* 2015; **58**: 358-362 [PMID: 25664716 DOI: 10.1097/DCR.0000000000000243]

21 **Japan Colonic Stent Safe Procedure Research (JCSSPR) Group**. CROSS: ColoRectal Obstruction Scoring System 2012. Available from: https://colon-stent.com/en

22 **Ohki T**, Yoshida S, Yamamoto M, Isayama H, Yamada T, Matsuzawa T, Saito S, Kuwai T, Tomita M, Shiratori T, Shimada M, Hirakawa T, Koizumi K, Saida Y. Determining the difference in the efficacy and safety of self-expandable metallic stents as a bridge to surgery for obstructive colon cancer among patients in the CROSS 0 group and those in the CROSS 1 or 2 group: a pooled analysis of data from two Japanese prospective multicenter trials. *Surg Today* 2020; **50**: 984-994 [PMID: 32025817 DOI: 10.1007/s00595-020-01970-3]

23 **Sloothaak DA**, van den Berg MW, Dijkgraaf MG, Fockens P, Tanis PJ, van Hooft JE, Bemelman WA; collaborative Dutch Stent-In study group. Oncological outcome of malignant colonic obstruction in the Dutch Stent-In 2 trial. *Br J Surg* 2014; **101**: 1751-1757 [PMID: 25298250 DOI: 10.1002/bjs.9645]

24 **Datye A**, Hersh J. Colonic perforation after stent placement for malignant colorectal obstruction--causes and contributing factors. *Minim Invasive Ther Allied Technol* 2011; **20**: 133-140 [PMID: 20929424 DOI: 10.3109/13645706.2010.518787]

25 **van Halsema EE**, van Hooft JE, Small AJ, Baron TH, García-Cano J, Cheon JH, Lee MS, Kwon SH, Mucci-Hennekinne S, Fockens P, Dijkgraaf MG, Repici A. Perforation in colorectal stenting: a meta-analysis and a search for risk factors. *Gastrointest Endosc* 2014; **79**: 970-982 [PMID: 24650852 DOI: 10.1016/j.gie.2013.11.038]

26 **Meisner S**, González-Huix F, Vandervoort JG, Repici A, Xinopoulos D, Grund KE, Goldberg P; Registry Group TW. Self-Expanding Metal Stenting for Palliation of Patients with Malignant Colonic Obstruction: Effectiveness and Efficacy on 255 Patients with 12-Month's Follow-up. *Gastroenterol Res Pract* 2012; **2012**: 296347 [PMID: 22761609 DOI: 10.1155/2012/296347]

27 **Saito S**, Yoshida S, Isayama H, Matsuzawa T, Kuwai T, Maetani I, Shimada M, Yamada T, Tomita M, Koizumi K, Hirata N, Kanazawa H, Enomoto T, Sekido H, Saida Y. A prospective multicenter study on self-expandable metallic stents as a bridge to surgery for malignant colorectal obstruction in Japan: efficacy and safety in 312 patients. *Surg Endosc* 2016; **30**: 3976-3986 [PMID: 26684205 DOI: 10.1007/s00464-015-4709-5]

28 **Khot UP**, Lang AW, Murali K, Parker MC. Systematic review of the efficacy and safety of colorectal stents. *Br J Surg* 2002; **89**: 1096-1102 [PMID: 12190673 DOI: 10.1046/j.1365-2168.2002.02148.x]

29 **Lee JM**, Byeon JS. Colorectal Stents: Current Status. *Clin Endosc* 2015; **48**: 194-200 [PMID: 26064818 DOI: 10.5946/ce.2015.48.3.194]

30 **Sebastian S**, Johnston S, Geoghegan T, Torreggiani W, Buckley M. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. *Am J Gastroenterol* 2004; **99**: 2051-2057 [PMID: 15447772 DOI: 10.1111/j.1572-0241.2004.40017.x]

31 **Matsuda A**, Yamada T, Matsumoto S, Shinji S, Ohta R, Sonoda H, Takahashi G, Iwai T, Takeda K, Sekiguchi K, Yoshida H. Systemic Chemotherapy is a Promising Treatment Option for Patients with Colonic Stents: A Review. *J Anus Rectum Colon* 2021; **5**: 1-10 [PMID: 33537495 DOI: 10.23922/jarc.2020-061]

32 **Imbulgoda A**, MacLean A, Heine J, Drolet S, Vickers MM. Colonic perforation with intraluminal stents and bevacizumab in advanced colorectal cancer: retrospective case series and literature review. *Can J Surg* 2015; **58**: 167-171 [PMID: 25799132 DOI: 10.1503/cjs.013014]

33 **Small AJ**, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest Endosc* 2010; **71**: 560-572 [PMID: 20189515 DOI: 10.1016/j.gie.2009.10.012]

34 **Zeng Z**, Liu Y, Wu K, Li D, Lai H, Zhang B. Efficacy and Safety of Fluoroscopy-Guided Self-Expandable Metal Stent Placement for Treatment of Malignant Colorectal Obstruction. *Dig Dis Sci* 2022 [PMID: 35653010 DOI: 10.1007/s10620-022-07557-x]

35 **Lee JH**, Emelogu I, Kukreja K, Ali FS, Nogueras-Gonzalez G, Lum P, Coronel E, Ross W, Raju GS, Lynch P, Thirumurthi S, Stroehlein J, Wang Y, You YN, Weston B. Safety and efficacy of metal stents for malignant colonic obstruction in patients treated with bevacizumab. *Gastrointest Endosc* 2019; **90**: 116-124 [PMID: 30797835 DOI: 10.1016/j.gie.2019.02.016]

36 **Han JG**, Wang ZJ, Zeng WG, Wang YB, Wei GH, Zhai ZW, Zhao BC, Yi BQ. Efficacy and safety of self-expanding metallic stent placement followed by neoadjuvant chemotherapy and scheduled surgery for treatment of obstructing left-sided colonic cancer. *BMC Cancer* 2020; **20**: 57 [PMID: 31992260 DOI: 10.1186/s12885-020-6560-x]

37 **Webster PJ**, Aldoori J, Burke DA. Optimal management of malignant left-sided large bowel obstruction: do international guidelines agree? *World J Emerg Surg* 2019; **14**: 23 [PMID: 31139245 DOI: 10.1186/s13017-019-0242-5]

38 **van Hooft JE**, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jiménez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A; European Society of Gastrointestinal Endoscopy. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2014; **46**: 990-1053 [PMID: 25325682 DOI: 10.1055/s-0034-1390700]

39 **Veld JV**, Amelung FJ, Borstlap WAA, Eise van Halsema E, Consten ECJ, Siersema PD, Ter Borg F, Silvester van der Zaag E, Fockens P, Bemelman WA, Elise van Hooft J, Tanis PJ; Dutch Snapshot Research Group. Changes in Management of Left-Sided Obstructive Colon Cancer: National Practice and Guideline Implementation. *J Natl Compr Canc Netw* 2019; **17**: 1512-1520 [PMID: 31805533 DOI: 10.6004/jnccn.2019.7326]

40 **Gavriilidis P**, Askari A, de'Angelis N, Gavriilidis EP, Wheeler J, Davies J. Appraisal of the Current Guidelines for Management of Malignant Left-Sided Colonic Obstruction Using the Appraisal of Guidelines Research and Evaluation II Instrument. *Dig Surg* 2021; **38**: 177-185 [PMID: 33756480 DOI: 10.1159/000514446]

41 **Allievi N**, Ceresoli M, Fugazzola P, Montori G, Coccolini F, Ansaloni L. Endoscopic Stenting as Bridge to Surgery *vs* Emergency Resection for Left-Sided Malignant Colorectal Obstruction: An Updated Meta-Analysis. *Int J Surg Oncol* 2017; **2017**: 2863272 [PMID: 28761765 DOI: 10.1155/2017/2863272]

42 **Saida Y**. Current status of colonic stent for obstructive colorectal cancer in Japan; a review of the literature. *J Anus Rectum Colon* 2019; **3**: 99-105 [PMID: 31583324 DOI: 10.23922/jarc.2019-009]

43 **Matsuda A**, Yamada T, Matsumoto S, Sakurazawa N, Kawano Y, Sekiguchi K, Matsutani T, Miyashita M, Yoshida H. Short-term outcomes of a self-expandable metallic stent as a bridge to surgery vs. a transanal decompression tube for malignant large-bowel obstruction: a meta-analysis. *Surg Today* 2019; **49**: 728-737 [PMID: 30798434 DOI: 10.1007/s00595-019-01784-y]

44 **Foo CC**, Poon SHT, Chiu RHY, Lam WY, Cheung LC, Law WL. Is bridge to surgery stenting a safe alternative to emergency surgery in malignant colonic obstruction: a meta-analysis of randomized control trials. *Surg Endosc* 2019; **33**: 293-302 [PMID: 30341649 DOI: 10.1007/s00464-018-6487-3]

45 **Katsuki R**, Jo T, Yasunaga H, Ishimaru M, Sakamoto T. Outcomes of self-expandable metal stent as bridge to surgery *vs* emergency surgery for left-sided obstructing colon cancer: A retrospective cohort study. *Am J Surg* 2021; **221**: 168-173 [PMID: 32600844 DOI: 10.1016/j.amjsurg.2020.06.012]

46 **Gorissen KJ**, Tuynman JB, Fryer E, Wang L, Uberoi R, Jones OM, Cunningham C, Lindsey I. Local recurrence after

stenting for obstructing left-sided colonic cancer. *Br J Surg* 2013; **100**: 1805-1809 [PMID: 24227368 DOI: 10.1002/bjs.9297]

47 **Uehara H**, Yamazaki T, Iwaya A, Kameyama H, Komatsu M, Hirai M. Comparison of the oncological outcomes of stenting as a bridge to surgery and surgery alone in stages II to III obstructive colorectal cancer: a retrospective study. *Ann Coloproctol* 2022; **38**: 235-243 [PMID: 34256426 DOI: 10.3393/ac.2020.01067.0152]

48 **Mege D**, Sabbagh C, Manceau G, Bridoux V, Lakkis Z, Momar D, Sielezneff I, Karoui M; AFC (French Surgical Association) Working Group. What is the Best Option Between Primary Diverting Stoma or Endoscopic Stent as a Bridge to Surgery with a Curative Intent for Obstructed Left Colon Cancer? *Ann Surg Oncol* 2019; **26**: 756-764 [PMID: 30623342 DOI: 10.1245/s10434-018-07139-0]

49 **Sabbagh C**, Browet F, Diouf M, Cosse C, Brehant O, Bartoli E, Mauvais F, Chauffert B, Dupas JL, Nguyen-Khac E, Regimbeau JM. Is stenting as "a bridge to surgery" an oncologically safe strategy for the management of acute, left-sided, malignant, colonic obstruction? *Ann Surg* 2013; **258**: 107-115 [PMID: 23324856 DOI: 10.1097/SLA.0b013e31827e30ce]

50 **Sabbagh C**, Chatelain D, Trouillet N, Mauvais F, Bendjaballah S, Browet F, Regimbeau JM. Does use of a metallic colon stent as a bridge to surgery modify the pathology data in patients with colonic obstruction? *Surg Endosc* 2013; **27**: 3622-3631 [PMID: 23572218 DOI: 10.1007/s00464-013-2934-3]

51 **Zhang S**, Liu G, Wu GH, Zhang SW, Zhao YJ, Xu J. Transanal decompression tube is superior to self-expandable metallic colonic stent for malignant colorectal obstruction: a retrospective study. *ANZ J Surg* 2022; **92**: 140-145 [PMID: 34636468 DOI: 10.1111/ans.17274]

52 **Maruthachalam K**, Lash GE, Shenton BK, Horgan AF. Tumour cell dissemination following endoscopic stent insertion. *Br J Surg* 2007; **94**: 1151-1154 [PMID: 17541987 DOI: 10.1002/bjs.5790]

53 **Yamashita S**, Tanemura M, Sawada G, Moon J, Shimizu Y, Yamaguchi T, Kuwai T, Urata Y, Kuraoka K, Hatanaka N, Yamashita Y, Taniyama K. Impact of endoscopic stent insertion on detection of viable circulating tumor cells from obstructive colorectal cancer. *Oncol Lett* 2018; **15**: 400-406 [PMID: 29391884 DOI: 10.3892/ol.2017.7339]

54 **Yoo RN**, Cho HM, Kye BH. Management of obstructive colon cancer: Current status, obstacles, and future directions. *World J Gastrointest Oncol* 2021; **13**: 1850-1862 [PMID: 35070029 DOI: 10.4251/wjgo.v13.i12.1850]

55 **Takahashi G**, Yamada T, Iwai T, Takeda K, Koizumi M, Shinji S, Uchida E. Oncological Assessment of Stent Placement for Obstructive Colorectal Cancer from Circulating Cell-Free DNA and Circulating Tumor DNA Dynamics. *Ann Surg Oncol* 2018; **25**: 737-744 [PMID: 29235008 DOI: 10.1245/s10434-017-6300-x]

56 **Cirocchi R**, Arezzo A, Sapienza P, Crocetti D, Cavaliere D, Solaini L, Ercolani G, Sterpetti AV, Mingoli A, Fiori E. Current Status of the Self-Expandable Metal Stent as a Bridge to Surgery Versus Emergency Surgery in Colorectal Cancer: Results from an Updated Systematic Review and Meta-Analysis of the Literature. *Medicina (Kaunas)* 2021; **57** [PMID: 33804232 DOI: 10.3390/medicina57030268]

57 **Arezzo A**, Balague C, Targarona E, Borghi F, Giraudo G, Ghezzo L, Arroyo A, Sola-Vera J, De Paolis P, Bossotti M, Bannone E, Forcignanò E, Bonino MA, Passera R, Morino M. Colonic stenting as a bridge to surgery *vs* emergency surgery for malignant colonic obstruction: results of a multicentre randomised controlled trial (ESCO trial). *Surg Endosc* 2017; **31**: 3297-3305 [PMID: 27924392 DOI: 10.1007/s00464-016-5362-3]

58 **Amelung FJ**, Borstlap WAA, Consten ECJ, Veld JV, van Halsema EE, Bemelman WA, Siersema PD, Ter Borg F, van Hooft JE, Tanis PJ; Dutch Snapshot Research Group. Propensity score-matched analysis of oncological outcome between stent as bridge to surgery and emergency resection in patients with malignant left-sided colonic obstruction. *Br J Surg* 2019; **106**: 1075-1086 [PMID: 31074507 DOI: 10.1002/bjs.11172]

59 **Veld JV**, Amelung FJ, Borstlap WAA, van Halsema EE, Consten ECJ, Siersema PD, Ter Borg F, van der Zaag ES, de Wilt JHW, Fockens P, Bemelman WA, van Hooft JE, Tanis PJ; Dutch Snapshot Research Group. Comparison of Decompressing Stoma *vs* Stent as a Bridge to Surgery for Left-Sided Obstructive Colon Cancer. *JAMA Surg* 2020; **155**: 206-215 [PMID: 31913422 DOI: 10.1001/jamasurg.2019.5466]

60 **Endo S**, Kumamoto K, Enomoto T, Koizumi K, Kato H, Saida Y. Comparison of survival and perioperative outcome of the colonic stent and the transanal decompression tube placement and emergency surgery for left-sided obstructive colorectal cancer: a retrospective multi-center observational study "The CODOMO study". *Int J Colorectal Dis* 2021; **36**: 987-998 [PMID: 33247313 DOI: 10.1007/s00384-020-03806-5]

61 **Kim SH**, Jang SH, Jeon HJ, Choi HS, Kim ES, Keum B, Jeen YT, Chun HJ, Kim J. Colonic stenting as a bridge to surgery for obstructive colon cancer: is it safe in the long term? *Surg Endosc* 2022; **36**: 4392-4400 [PMID: 35075522 DOI: 10.1007/s00464-021-08789-0]

62 **Amelung FJ**, Burghgraef TA, Tanis PJ, van Hooft JE, Ter Borg F, Siersema PD, Bemelman WA, Consten ECJ. Critical appraisal of oncological safety of stent as bridge to surgery in left-sided obstructing colon cancer; a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2018; **131**: 66-75 [PMID: 30293707 DOI: 10.1016/j.critrevonc.2018.08.003]

63 **Enomoto T**, Saida Y, Takabayashi K, Nagao S, Takeshita E, Watanabe R, Takahashi A, Nakamura Y, Asai K, Watanebe M, Nagao J, Kusachi S. Open surgery *vs* laparoscopic surgery after stent insertion for obstructive colorectal cancer. *Surg Today* 2016; **46**: 1383-1386 [PMID: 27017599 DOI: 10.1007/s00595-016-1331-7]

64 **Takeyama H**, Danno K, Nishigaki T, Yamashita M, Yamazaki M, Yamakita T, Nishihara A, Taniguchi H, Mizutani M, Nakamichi I, Yura M, Ikeda K, Oka Y. Robot-assisted laparoscopic surgery after placing a self-expanding metallic stent for malignant rectal obstruction: a case report. *Surg Case Rep* 2019; **5**: 156 [PMID: 31654242 DOI: 10.1186/s40792-019-0719-1]

65 **Li JW**, Ngu JC, Lim KR, Tay SW, Jiang B, Wijaya R, Yusof S, Ong CJ, Kwek ABE, Ang TL. Colonic stenting in acute malignant large bowel obstruction - an audit of efficacy and safety in a tertiary referral centre in Singapore. *Singapore Med J* 2021 [PMID: 34600451 DOI: 10.11622/smedj.2021127]

66 **Sato R**, Oikawa M, Kakita T, Okada T, Abe T, Yazawa T, Tsuchiya H, Akazawa N, Yoshimachi S, Ohira T, Harada Y, Okano H, Ito K, Tsuchiya T. A longer interval after stenting compromises the short- and long-term outcomes after curative surgery for obstructive colorectal cancer. *Surg Today* 2022; **52**: 681-689 [PMID: 34648067 DOI: 10.1007/s00595-021-02385-4]

67 **Broholm M**, Kobborg M, Frostberg E, Jeppesen M, Gögenür I. Delay of surgery after stent placement for resectable

malignant colorectal obstruction is associated with higher risk of recurrence. *Int J Colorectal Dis* 2017; **32**: 513-516 [PMID: 27853888 DOI: 10.1007/s00384-016-2705-4]

68 **Veld JV**, Kumcu A, Amelung FJ, Borstlap WAA, Consten ECJ, Dekker JWT, van Westreenen HL, Siersema PD, Ter Borg F, Kusters M, Bemelman WA, de Wilt JHW, van Hooft JE, Tanis PJ; Dutch Snapshot Research Group. Time interval between self-expandable metal stent placement or creation of a decompressing stoma and elective resection of left-sided obstructive colon cancer. *Endoscopy* 2021; **53**: 905-913 [PMID: 33339059 DOI: 10.1055/a-1308-1487]

69 **Quinn PL**, Arjani S, Ahlawat SK, Chokshi RJ. Cost-effectiveness of palliative emergent surgery *vs* endoscopic stenting for acute malignant colonic obstruction. *Surg Endosc* 2021; **35**: 2240-2247 [PMID: 32430522 DOI: 10.1007/s00464-020-07637-x]

70 **Kaida T**, Doi K, Yumoto S, Kinoshita S, Takeyama H, Ishiodori H, Baba H. Cost-effectiveness of self-expandable metallic stents as bridge to surgery for obstructive colorectal cancer. *Int J Clin Oncol* 2021; **26**: 1485-1491 [PMID: 33937958 DOI: 10.1007/s10147-021-01928-6]

71 **Singh H**, Latosinsky S, Spiegel BM, Targownik LE. The cost-effectiveness of colonic stenting as a bridge to curative surgery in patients with acute left-sided malignant colonic obstruction: a Canadian perspective. *Can J Gastroenterol* 2006; **20**: 779-785 [PMID: 17171197 DOI: 10.1155/2006/307324]

72 **Suen MK**, Zahid A, Young JM, Rodwell L, Solomon MJ, Young CJ. How to decide to undertake a randomized, controlled trial of stent or surgery in colorectal obstruction. *Surgery* 2015; **157**: 1137-1141 [PMID: 25796417 DOI: 10.1016/j.surg.2015.01.022]

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ORIGINAL ARTICLE

Basic Study

Identification of a three-gene prognostic signature for radioresistant esophageal squamous cell carcinoma

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Abstract

BACKGROUND

Esophageal squamous cell carcinoma (ESCC) is causing a high mortality rate due to the lack of efficient early prognosis markers and suitable therapeutic regimens. The prognostic role of genes responsible for the acquisition of radioresistance in ESCC has not been fully elucidated.

AIM

To establish a prognostic model by studying gene expression patterns pertinent to radioresistance in ESCC patients.

METHODS

Datasets were obtained from the Gene Expression Omnibus and The Cancer Genome Atlas databases. The edgeR, a Bioconductor package, was used to analyze mRNA expression between different groups. We screened genes specifically responsible for radioresistance to estimate overall survival. Pearson correlation analysis was performed to confirm whether the expression of those genes correlated with each other. Genes contributing to radioresistance and overall survival were assessed by the multivariate Cox regression model through the calculation of βi and risk score using the following formula: $\sum_{i=1}^{n} \beta i \times \mathrm{PSI}$.

RESULTS

We identified three prognostic mRNAs (cathepsin S [*CTSS*], cluster of differentiation 180 [*CD180*], and SLP adapter and CSK-interacting membrane protein [*SCIMP*]) indicative of radioresistance. The expression of the three identified mRNAs was related to each other ($r > 0.70$ and $P < 0.05$). As to 1-year and 3-year overall survival prediction, the area under the time-dependent receiver operating characteristic curve of the signature consisting of the three mRNAs was 0.716 and 0.841, respectively. When stratifying patients based on the risk score derived from the signature, the high-risk group exhibited a higher death risk and shorter survival time than the low-risk group ($P < 0.0001$). Overall survival of the low-risk patients was significantly better than that of the high-risk patients ($P = 0.018$).

CONCLUSION

We have developed a novel three-gene prognostic signature consisting of *CTSS, CD180*, and *SCIMO* for ESCC, which may facilitate the prediction of early prognosis of this malignancy.

Key Words: Esophageal squamous cell carcinoma; CTSS; CD180; SCIMP; Radioresistance; TNM stage; Prognosis

Core Tip: The current study identified a novel three-gene prognostic signature consisting of *CTSS, CD180*, and *SCIMO* for esophageal squamous cell carcinoma, which may facilitate the prediction of early prognosis of this malignancy.

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INTRODUCTION

Esophageal cancer is one of the most commonly occurring gastrointestinal tumors and ranks 7th in incidence and 6th in death among all malignancies worldwide. The highest incidence rate was reported in China[1]. Esophageal cancer includes two main pathological types, namely, esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC), and 88% of ESCC cases originate in central and southern Asia[2]. Surgery is the conventional method of treatment for early-stage esophageal cancer patients. Neoadjuvant radiotherapy is also reported to be a crucial therapeutic modality for treating advanced stage ESCC patients[3]. However, the differences in sensitivity of each patient to radiation therapy result in variable prognoses among ESCC patients. ESCC is an aggressive malignancy with a poor overall survival[4]. The available staging system is not very satisfactory in predicting the treatment outcome in ESCC patients, and the application of cancer genomics to predict clinical outcomes may improve the treatment of ESCC[5,6].

Tumor radiotherapy can induce either direct damage to DNA by inducing DNA double-strand breaks, or indirectly modulate cell signaling cascades to foster tumor cell death[7]. However, the clinical outcomes of radiotherapy in most esophageal tumor patients predominantly depend on the inherent sensitivity of tumor cells to radioactive rays. Furthermore, tumor cell insensitivity can lead to the occurrence of radioresistance, which involves several cellular mechanisms including cell cycle checkpoint regulation[8], stemness acquisition[9,10], epithelial mesenchymal transformation (EMT)[11], and activation of multiple pro-survival and pro-proliferation signaling pathways[12,13]. Furthermore, radioresistance is also mediated by tumor-associated microenvironment factors, such as hypoxia-

induced HIF-1 signaling factors[14,15], tumor-associated fibroblasts (CAFs)[16], and tumor-associated macrophages[17,18]. Hence, radioresistance is one of the significant reasons for the failure of radiotherapy in ESCC patients. High-throughput sequencing technology is a promising novel approach to identify genes that are related to tumor radioresistance in ESCC. Maher *et al*[19] identified a set of five genes including *EPB41L3, RTKN, STAT5B, NMES1*, and *RNPC1* as biomarkers for response to neoadjuvant radiotherapy in esophageal cancer. Overexpression of PTK7 can activate NF-kB to enhance raidoresistance in radiosensitive ESCC cells[20]. Transcriptome analysis delineated that the *MALAT1-ATG9B* and *DDIT4-MB-PLAT* genes could regulate radioresistance in *in vitro* models of ESCC cells by modulation of autophagy and hypoxia pathways[21]. The prognostic role and underlying genomic pathways pertinent to the acquisition of radioresistance in ESCC patients have not yet been fully unraveled. Therefore, it is crucial to identify biomarkers and genes pertaining to radioresistance in ESCC for selecting novel therapeutic modalities to mitigate radioresistance in this malignancy.

The current study identified mRNAs as potential radioresistance markers in ESCC cells with the aid of merged mRNA data collected from the Gene Expression Omnibus (GEO) and Cancer Genome Atlas (TCGA) databases. The study identified a three-gene signature, including *CTSS, CD180*, and *SCIMP*, that may predict the development of radioresistance in ESCC cells. Furthermore, we constructed a prognostic model for radioresistant ESCC based on the risk scores derived from clinical features and the three-gene signature.

MATERIALS AND METHODS

GEO database search: Identifying 'radioresistance-promoting mRNAs'

Primarily, the microarray profiles in GSE81812 dataset pertaining to 'non-radiated KYSE-180 cells' and "12 and 30 Gy radiated KYSE-180 cells" were downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/) to identify mRNAs contributing to radioresistance in ESCC cells. The edgeR package (www.bioconductor.org/packages/release/bioc/html/edgeR.html) was used to analyze the differential expression of mRNAs between different groups ('0 Gy group *vs* 12 Gy group' and '0 Gy group *vs* 30 Gy group') to identify genes related to radioresistance. The cutoff parameters were false discovery rate < 0.05 and $|\text{Log}_2 \text{ fold change}| > 2$.

TCGA database search: Identification of 'radioresistance-promoting mRNAs' associated with overall survival

Gene expression profile and clinical information of ESCC patients in the TCGA database were downloaded (https://gdc-portal.nci.nih.gov/). Overall survival rates were determined to ascertain the prognostic significance of the identified radioresistance promoting mRNAs in the TCGA database; the overall survival rates were analyzed by using survival package in R through Kaplan-Meier analysis and finally compared using the Log-rank test and Cox proportional hazards regression analysis. Then, radioresistance-promoting mRNAs associated with overall survival were screened.

Multivariate Cox regression analysis: Construction of prognostic model based on 'radioresistance-promoting mRNAs' associated with overall survival

The association of radioresistance-promoting mRNAs with overall survival was estimated using the multivariate Cox regression model, adjusted for age, gender, grade, and stage, to calculate βi. The forest plot was plotted to exhibit the hazards regression (HR) of the multivariate Cox regression model results. Later, risk score was estimated by using the following formula: $\sum_{i=1}^{n} \beta i \times \text{PSI}$. By using the maximally selected rank statistics from the 'survminer' package in R, all samples were divided into a low-risk group and a high-risk group subsequently, and survival analysis was conducted to assess prognosis differences between the two groups.

Confirmation of relationship of 'radioresistance-promoting mRNAs' with overall survival, tumor stage, and tumor grade

Pearson correlation coefficients ($P < 0.05$) were calculated using r.test () in R to confirm whether the identified radioresistance-associated mRNAs were typically related to the stage and grade of ESCC. The results are shown in violin plots.

Kyoto Encyclopedia of Genes and Genomes pathway analysis

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of mRNAs associated with radioresistance in ESCC was performed using the ClusterProfile package (http://www.bioconductor.org/packages/release/bioc/html/clusterProfiler.html) for a more comprehensive understanding of biological features. A P value < 0.05 was set as the cut-off criterion in the KEGG pathway. Data pertinent to KEGG pathway analysis is attached as a supporting file.

Statistical analysis

Statistical analyses were executed with the aid of SPSS 22.0 software (IBM, Chicago, IL, United States) and R version 3.6.0. Overall survival rate was estimated using the Kaplan-Meier method. Multivariate Cox proportional HR analysis was executed to identify prognostic factors (the three-gene signature, age, gender, tumor stage, and tumor grade). Differences between groups were compared using the Student's *t*-test or paired samples *t*-test. $P < 0.05$ was considered to have statistical significance.

RESULTS

GEO database search of mRNA expression profiles to identify radioresistance-promoting mRNAs

The gene count data of expression profiles of 22456 mRNAs in 41 samples of 0 Gy, 92 samples of 12 Gy, and 89 samples of 30 Gy were obtained from the GSE81812 dataset downloaded from GEO. We identified upregulation of 1168 mRNAs in the '0 Gy group *vs* 12 Gy group' comparison and 497 mRNAs in the '0 Gy group *vs* 30 Gy group' comparison by using the edgeR package. To distinguish the differentially expressed mRNAs at different X-ray levels, the top 50 mRNAs are shown in a heatmap and principal component analysis (PCA) was performed (Figure 1A-D). A total of 379 intersection mRNAs were identified from the 0-12 Gy and 0-30 Gy comparisons as radioresistance associated genes.

Prognostic significance of radioresistance-promoting mRNAs from TCGA database

Log-rank test and Cox proportional hazards regression were adjusted for other confounding factors such as gender, age, stage, and grade. These statistical analyses were used to screen for prognostic genes, and a total of 5293 mRNAs were selected. Among them, 44 mRNAs were significantly associated with radioresistance. We selected 23 mRNAs that were negatively correlated with prognosis for further analysis. The intersection of radioresistant prognostic mRNAs is visualized in a Venn diagram (Figure 1E).

Determination of correlations among radioresistance-promoting mRNAs

For the 23 mRNAs mentioned above, we primarily investigated whether their expression correlated with each other based on the data in the TCGA database. Although they were expressed at different levels in ESCC patients, the results showed strong correlations among three mRNAs, namely, *CTSS*, *CD180*, and *SCIMP* ($r > 0.70$ and $P < 0.05$). The correlations of 23 mRNAs are shown in a heatmap (Figure 2A). Hence, we selected these three mRNAs as radioresistance-promoting mRNAs of interest. Correlations of these three mRNAs are shown in a scattergram (Figure 2B-D).

Establishment of a gene signature as prognostic model for radioresistance

To explore the potential prognostic value of the above three mRNAs pertinent to radioresistance, we evaluated the overall survival rates of ESCC patients based on the expression patterns of these three mRNAs based on the data in the TCGA database by using Kaplan-Meier curves. As shown in Figure 3A, their low expression was associated with a good overall survival (TCGA database), and the median survival time was statistically significant ($P < 0.05$) for all the three mRNAs.

Subsequently, the connection between the three-gene signature and overall survival was explored through multivariate Cox regression model adjusted for patient age, gender, tumor grade, and tumor stage, for which, the HR with 95% confidence interval was depicted through the forest plot (Figure 3B). ROC analysis for the model is shown in Figure 3C (area under the curve: 0.716 and 0.841 for 1- and 3-year survival, respectively). Accordingly, the risk score of each patient was calculated, and all the patients were divided into either a high risk group or a low risk group based on the risk score.

The patients of the high-risk group exhibited a 'higher death risk and shorter survival time' than the patients in the low-risk group; the heatmap of the three genes (*CTSS, CD180*, and *SCIMP*) showed that the high-risk patients typically had higher expression of these genes than the low-risk patients (Figure 3D-F). The Kaplan-Meier curves revealed that the low-risk patients typically with low expression of these three genes exhibited a good overall survival (Figure 3G).

External validation based on GEO dataset

To further validate the prognostic value of the three mRNAs, GSE53625 dataset was downloaded from the GEO database. As shown in Figure 4A, downregulation of *SCIMP* expression was associated with a good survival outcome. When patients were divided into two groups based on *CTSS* expression, there was no statistically significant difference in their survival. CD180 expression also showed no significant correlation with survival. In the same manner, the risk score of GEO samples was calculated, and the overall survival of patient samples in the low-risk group was also higher than that of patient samples in the high-risk group (Figure 4B). The risk curve, scatter plot, and heatmap results were also similar to those obtained based on TCGA dataset (Figure 4C-E).

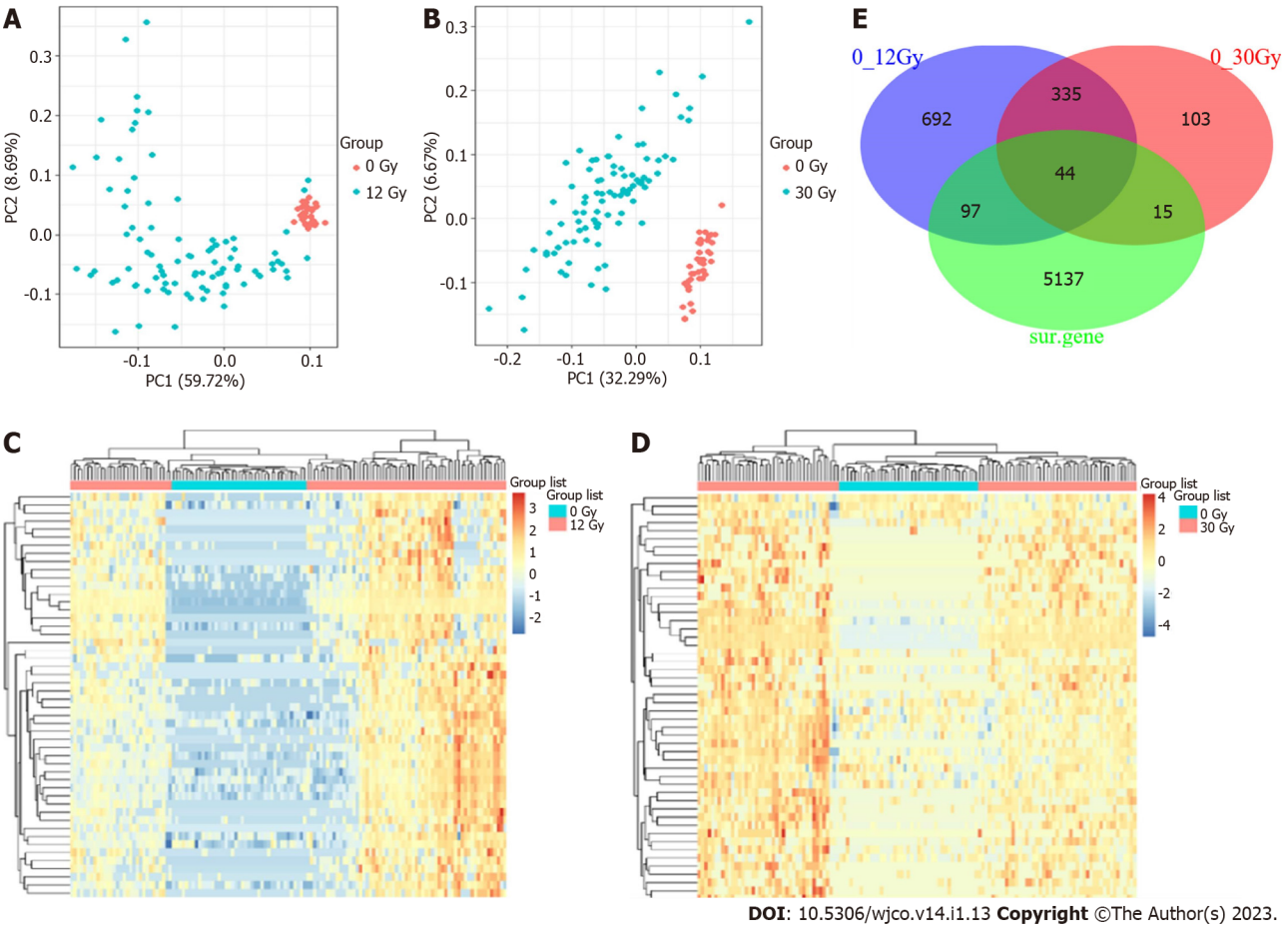

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Figure 1 Comparative principal component analysis and heatmap analysis of up-regulated mRNAs between non-radiated and radiated KYSE-180 cell samples. A and B: Principal component analysis. Samples were clustered into two groups: 0 Gy group *vs* 12 Gy group (A) and 0 Gy group *vs* 30 Gy group (B); C and D: Heatmap analysis. Upregulated genes are indicated in red whereas downregulated ones are indicated in green. The expression of mRNAs in radiated samples was comparatively higher than that in non-radiated samples: 0 Gy group *vs* 12 Gy group (C) and 0 Gy group *vs* 30 Gy group (D); E: Venn diagram of radioresistance-promoting mRNAs associated with prognosis in esophageal squamous cell carcinoma.

Association of the three mRNAs with pathological grade and tumor-node-metastasis stage

We next explored the association between the three radioresistance-promoting mRNAs and pathological grade (Figure 5A-C) and tumor-node-metastasis (TNM) stage (Figure 5D-F). *CTSS, CD180*, and *SCIMP* exhibited significantly higher expression in advanced pathological grades (2-3 *vs* 1) and tumor stages (II-IV *vs* I).

Functional characteristics of CTSS, CD180, and SCIMP mRNAs

To further explore the underlying biological features of the three mRNAs in ESCC, we performed Pearson correlation between the three mRNAs, namely, *CTSS, CD180*, and *SCIMP*, and the other mRNAs to identify co-expressed mRNAs. A total of 539 mRNAs were selected for KEGG pathway enrichment analysis ($P < 0.01$, $r > 0.4$). Our results showed that the co-expressed mRNAs were mainly enriched in 50 pathways, including NF-kB, JAK-STAT, cell adhesion molecules signaling, and PD-L1 expression & PD-1 checkpoint pathways (Figure 6).

DISCUSSION

Prolonged and fractionated irradiation during radiotherapy in ESCC patients could confer radioresistance and result in distant metastasis, which may lead to treatment failure[22,23]. CAFs can foster radioresistance in ESCC tumor cells through the long noncoding RNA DNM3OS by modulating the PDGFβ/PDGFRβ/FOXO1 signaling pathway, suggesting that CAFs-promoted DNM3OS could be a crucial target to reverse radioresistance in ESCC tumor cells. A study by Zhao *et al*[24] in 2020, showed that three genes (*FOXL2, TCF4*, and *NR2F2*) exhibited a significant correlation with the prognosis of endometrial carcinoma; biological pathways associated with the low expression of these three genes were significantly enriched in cell cycle and fatty acid metabolism of cancer cells. However, there is

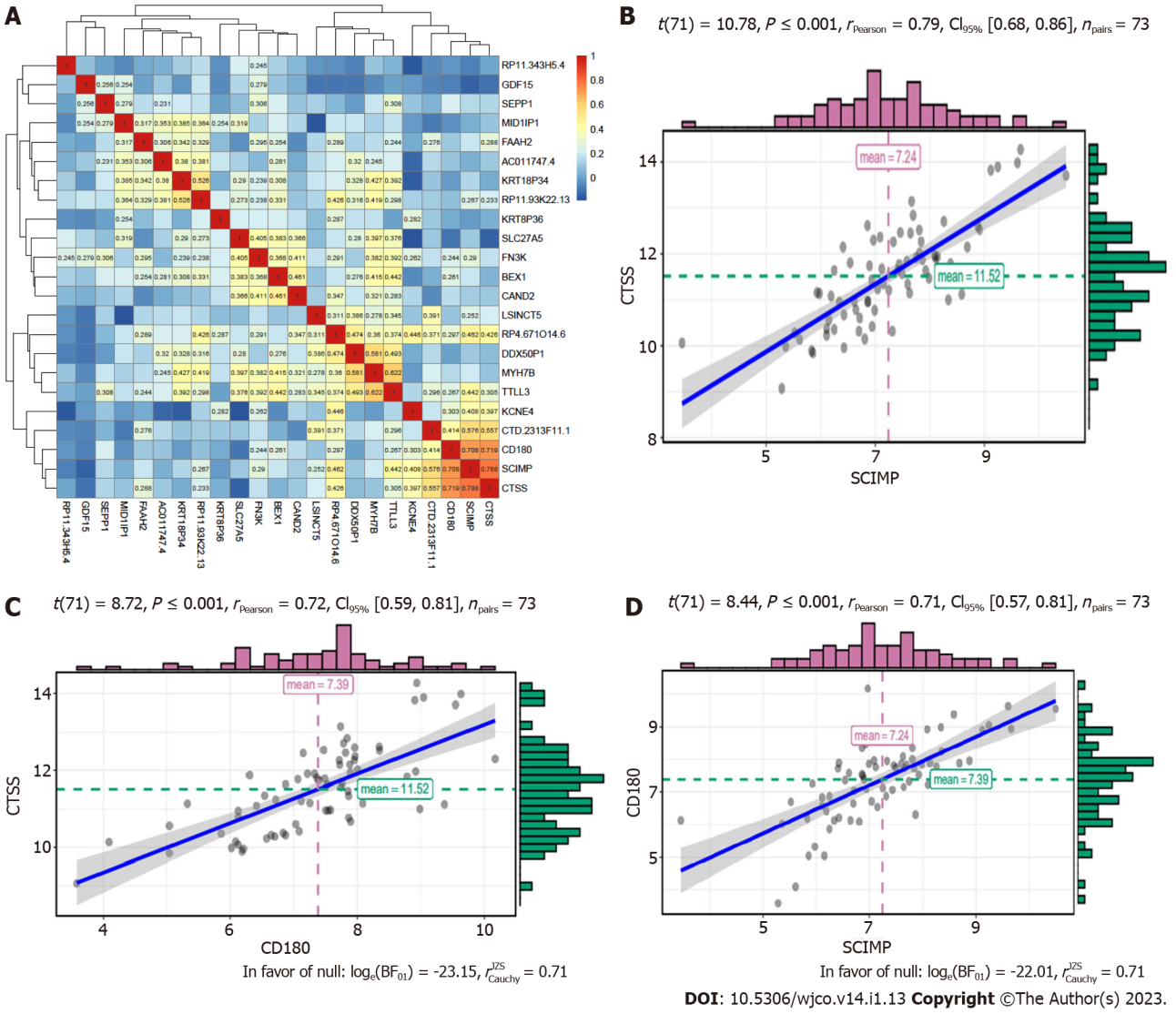

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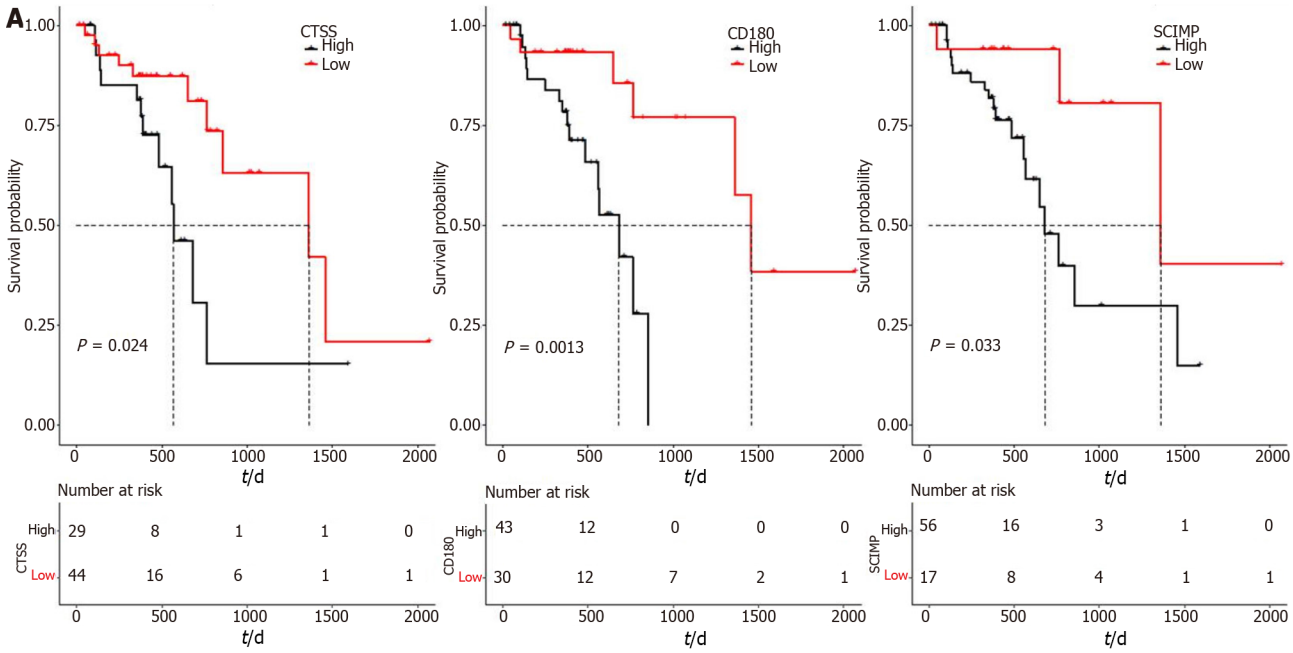
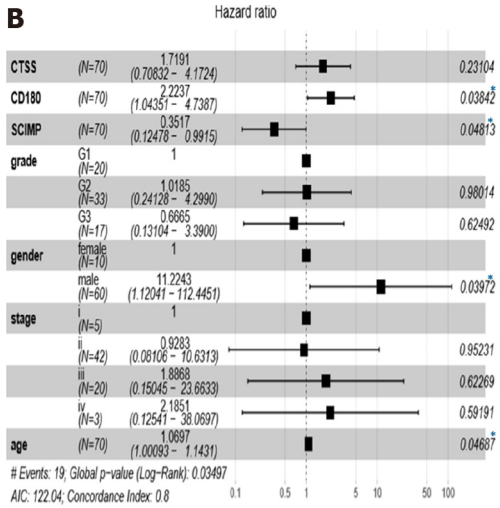
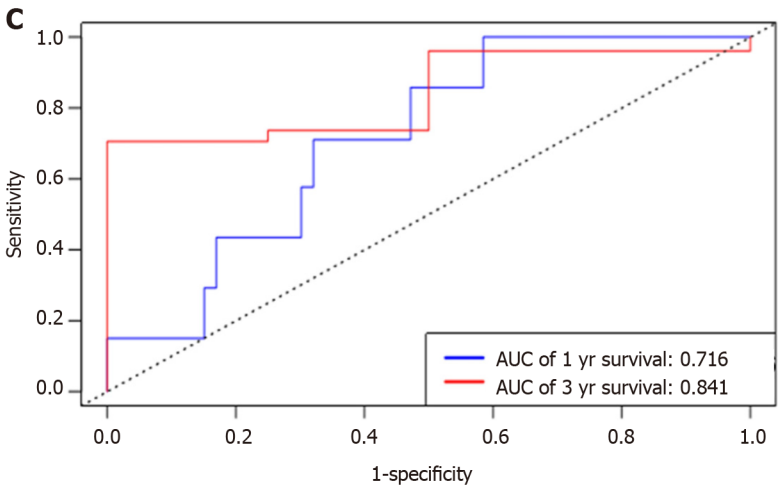
Figure 2 Heatmap and scattergram depicting the correlations of mRNAs. A: Heatmap showing correlations of 23 mRNAs contributing to radioresistance; B-D: Scattergram showing correlations between two of the three mRNAs: *CTSS vs SCIMP* (B), *CTSS vs CD180* (C), and *CD180 vs SCIMP* (D).

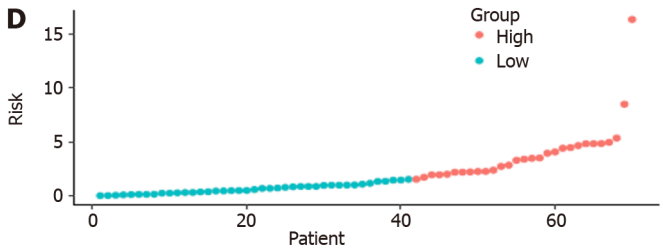
limited evidence to validate the gene signatures involved in conferring radioresistance in ESCC patients to delineate accurate and efficient disease prognosis[25]. Ma *et al*[26] demonstrated that HMGB1 promotes radioresistance through the activation of autophagy. Furthermore, differentially expressed genes (DEGs) including '*CFLAR, LAMA5, ITGA6, ITGB4*, and *SDC4*' in five signaling cascades (PI3K-AKT pathway, CYCS gene-based apoptosis pathway, S100AX–AKT3-related pathway, SDC4 and HSPG2 pathway, and mTOR signaling pathway) were reported to be associated with radioresistance in *in vitro* ESCC models, and tissue biopsies of ESCC patients[27]. In the present study, we, for the first time, constructed a risk score model based on three radioresistance-associated mRNAs (*CTSS, CD180*, and *SCIMP*) and clinical features of ESCC patients; this model could facilitate oncologists to predict overall survival of ESCC patients with acquired radioresistance in radiotherapy.

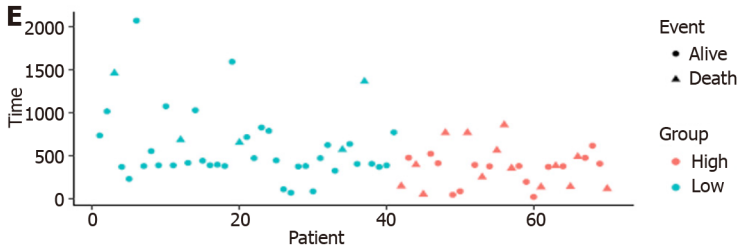
A research study showed that the insulin-like growth factor 2 mRNA-binding protein 3 can contribute to the development of radioresistance in ESCC[28]. miR-205 promotes radioresistance in ESCC typically through enhancing DNA repair, impairing apoptosis, and stimulating EMT[29]. Another factor *i.e.*, eEF2K, could foster the progression of radioresistance in ESCC[30]. In our study, the involvement of three mRNAs (*CTSS, CD180*, and *SCIMP*) in radioresistance was analyzed through the transcriptome profiling of ESCC samples between non-radiated KYSE-180 cells and 12 or 30 Gy far infrared radiation-treated KYSE-180 cells and by constructing a risk score model. However, the overall survival information in GSE81812 dataset is unavailable, so we conducted univariate and multivariate Cox regression analysis based on the TCGA database, and identified 49 radioresistance-associated mRNAs associated with survival, of which 23 were inversely correlated with survival. After comprehensive correlation analysis, we selected three radioresistance-associated mRNAs (*CTSS, CD180*, and *SCIMP*) that were strongly correlated with each other based on the data in the TCGA database. Subramanian *et al*[31] deciphered that the well-developed genomic signatures are significantly


A
CTSS
High
Low
Survival probability
P = 0.024
t/d
Number at risk
High 29 8 1 1 0
Low 44 16 6 1 1
CD180
P = 0.0013
High 43 12 0 0 0
Low 30 12 7 2 1
SCIMP
P = 0.033
High 56 16 3 1 0
Low 17 8 4 1 1


B
Hazard ratio
CTSS (N=70) 1.7191 (0.70832 - 4.1724) 0.23104
CD180 (N=70) 2.2237 (1.04351 - 4.7387) 0.03842
SCIMP (N=70) 0.3517 (0.12478 - 0.9915) 0.04813
grade G1 (N=20) 1
G2 (N=33) 1.0185 (0.24128 - 4.2990) 0.98014
G3 (N=17) 0.6665 (0.13104 - 3.3900) 0.62492
gender female (N=10) 1
male (N=60) 11.2243 (1.12041 - 112.4451) 0.03972
stage i (N=5) 1
ii (N=42) 0.9283 (0.08106 - 10.6313) 0.95231
iii (N=20) 1.8868 (0.15045 - 23.6633) 0.62269
iv (N=3) 2.1851 (0.12541 - 38.0697) 0.59191
age (N=70) 1.0697 (1.00093 - 1.1431) 0.04687
Events: 19; Global p-value (Log-Rank): 0.03497
AIC: 122.04; Concordance Index: 0.8


C
Sensitivity
1-specificity
AUC of 1 yr survival: 0.716
AUC of 3 yr survival: 0.841


D
Group
High
Low
Risk
Patient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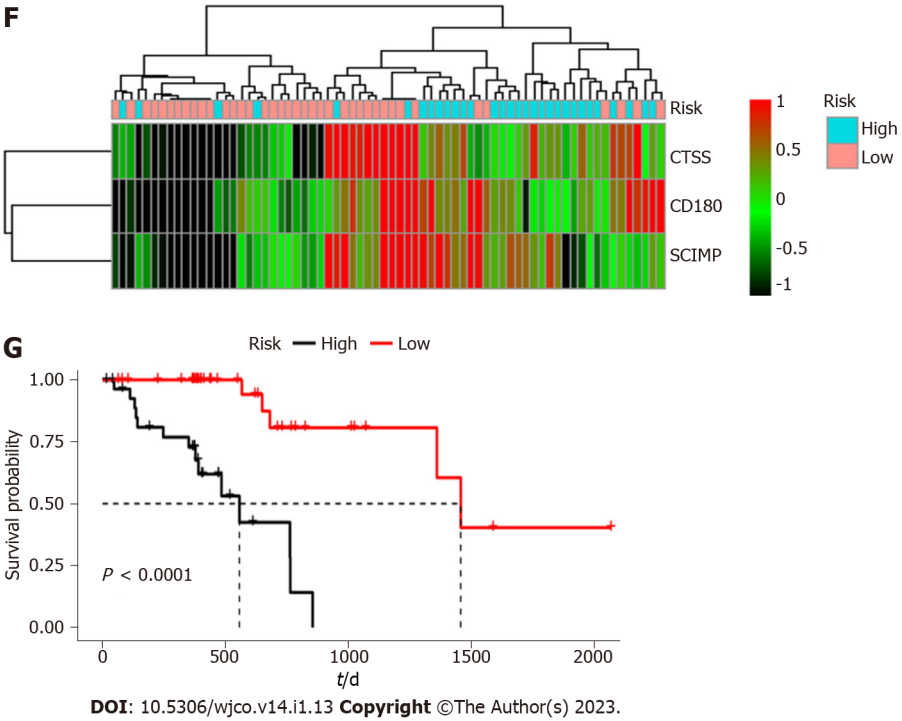

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Figure 3 Kaplan-Meier curves. A: Kaplan-Meier survival curves by expression of *CTSS*, *SCIMP*, and *CD180* based on data from TCGA database; B: Forest plot established with a hazard ratio calculated through multivariate Cox regression model adjusting for age, gender, grade, and stage ($P < 0.05$); C: Receiver operating characteristic analysis for 1- and 3-year overall survival prediction; D-F: Risk score distribution for patients in high risk group and low risk group. *SCIMP*, *CD180*, and *CTSS* had higher expression in high risk group than in low risk group; G: Kaplan–Meier survival curves for the high risk group and low risk group.

beneficial for improving clinical outcomes in ESCC patients. Results of the overall survival of patients in this study suggested that patients with a higher risk score exhibited a poorer prognosis. Moreover, we downloaded the GSE53625 dataset as independent validation data to validate the prognostic role of the three-mRNA signature. Our result confirmed that the risk score model could also predict the survival outcome based on the external validation datasets.

Among the three mRNAs investigated, *CTSS* encodes a cysteine protease. Seo *et al*[32] showed radiation-induced *CTSS* overexpression, which can consequently promote radioresistance, and knockdown of *CTSS* could induce impairment of radioresistance by modulating the ROS-IFN-γ pathway[32]. Additionally, a plethora of research studies have found that CTSS is particularly involved in modulating autophagy pathways[33], PI3K/Akt and Ras/Raf/MAPK signaling pathways[34], and EGFR-ERK signaling pathway[35] as these signaling cascades are more or less involved in conferring radioresistance. However, there are no reports available in the literature to delineate that CD180 and SCIMP are involved in causing radioresistance in ESCC patients. CD180 belongs to the family of Toll-like receptors. Its expression has been reported to be associated with acute or chronic leukemia[36]. *SCIMP* encodes a transmembrane adaptor protein that shapes host defense and inflammation *via* direct modulation of TLR4[37].

A report by Yang *et al*[27] described the activation of the PI3K-Akt signaling pathway (KEGG ID: hsa05200) with upregulation of DEGs such as *LAMA5, LAMB2, LAMB3, ITGA6,* and *ITGB4* at 12-Gy and 30-Gy fractionated irradiation. Thus, PI3K-Akt is reported to be involved in protecting KYSE-180 cells from undergoing apoptosis after irradiation. *CYCS* gene-based apoptosis pathway (KEGG ID: hsa04210) is impaired after 12-Gy irradiation due to the induction of *CYCS* downregulation. KEGG pathway analysis of S100AX–AKT3 signaling depicted that the activation of this pathway could enhance the migration and metastasis of HSCC KYSE-180-12 Gy and KYE-180-30 Gy cells[27,38]. SDC4 and HSPG2 [KEGG ID: hsa05205] are two proteoglycans that were reported to be upregulated during the irradiation of KYSE-180 cells at doses of 12 Gy and 30 Gy. These genes are responsible for tumor cell invasion and metastasis[27]. In the present study, KEGG pathway analysis was performed to clarify the underlying mechanisms of the three mRNAs contributing to the radioresistance of ESCC cells. Our results showed that these mRNAs were mainly enriched in pathways that are related to radioresistance, such as the JAK-STAT signaling pathway[39] and NF-kB signaling pathway[40]. Our results also demonstrated the radioresistance-promoting ability of these three mRNAs. Besides, these mRNAs were enriched in immune-related pathways, such as antigen processing and presentation, cytokine-cytokine receptor interaction, and Th17 cell differentiation. Hence, these three radioresistance-associated mRNAs might be involved in the regulation of immune pathways contributing to ESCC cell radioresistance.

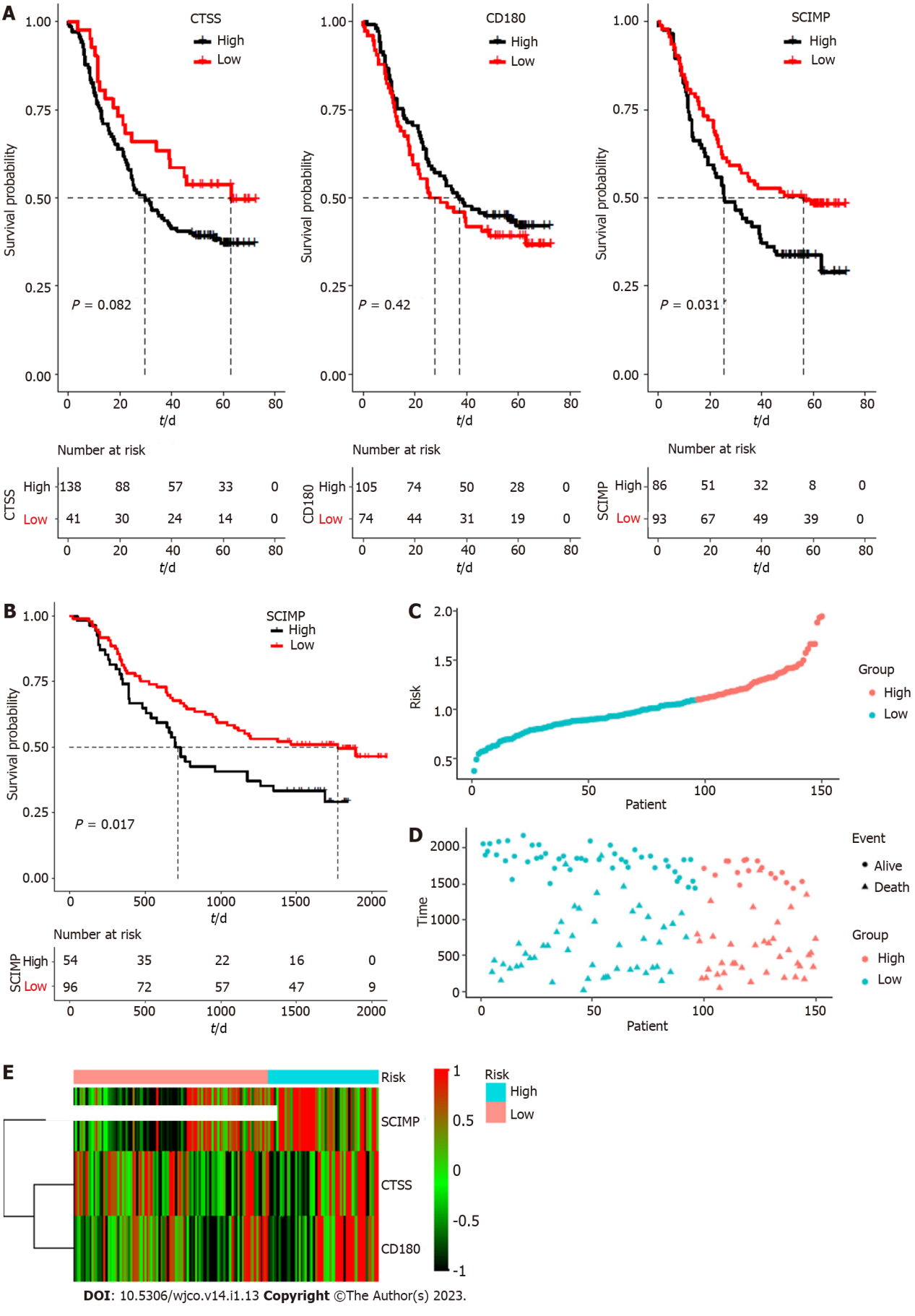

Figure 4 Validation of prognostic value of the three mRNAs based on dataset downloaded from the Gene Expression Omnibus database.

A: Kaplan–Meier survival curves for *SCIMP*, *CD180*, and *CTSS* based on GSE53625 dataset; B: Kaplan–Meier survival curves for the high risk group and low risk

group; C-E: Risk score distribution for patients in high risk group and low risk group. *SCIMP*, *CD180*, and *CTSS* had higher expression in high risk group than in low risk group.

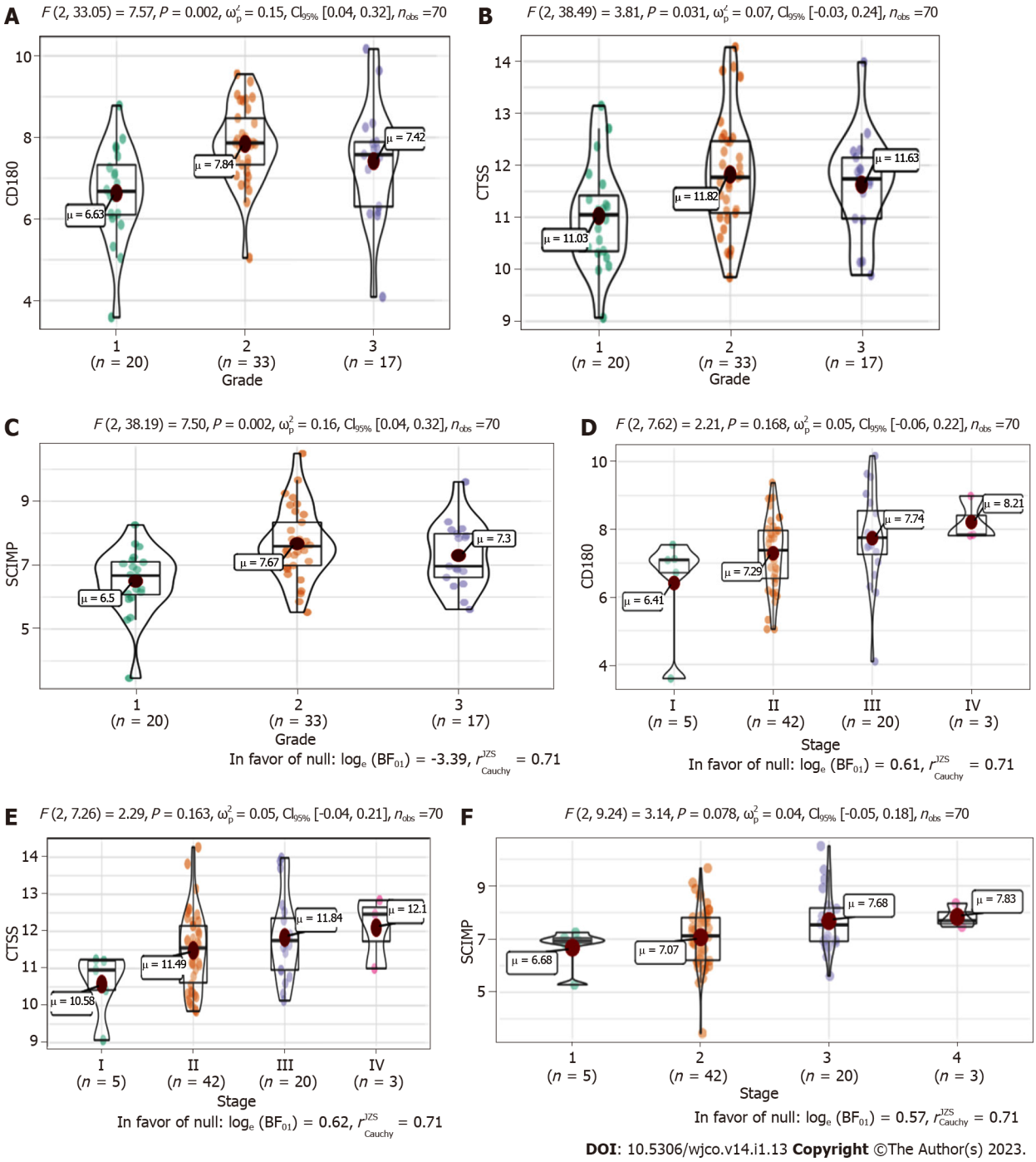

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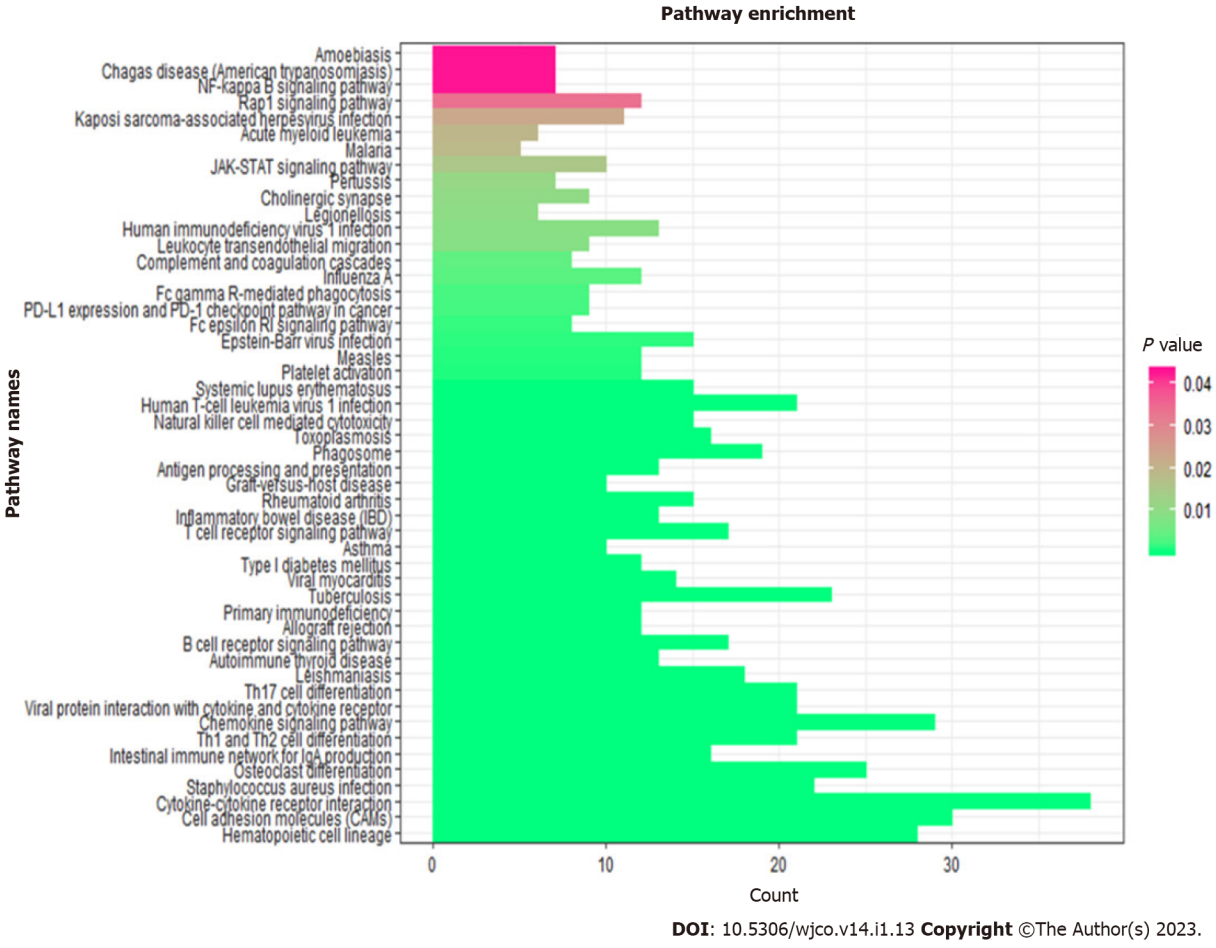
Figure 5 Association of the three radioresistance-promoting mRNAs (*CTSS*, *CD180*, and *SCIMP*) with tumor characteristics. A-C: Box plots showing a positive correlation of *SCIMP*, *CD180*, and *CTSS* with pathological grade; D-F: Box plots showing a positive correlation of *SCIMP*, *CD180*, and *CTSS* with tumor-node-metastasis stage.

CONCLUSION

In summary, our study proved that CTSS, CD180 and SCIMP can promote the development of radioresistance in ESCC patients. The novel three-gene signature developed based on the three genes can be used as a prognostic model to predict the prognosis of patients with radioresistant ESCC.



DOI: 10.5306/wjco.v14.i1.13

Figure 6 Kyoto Encyclopedia of Genes and Genomes enrichment analysis of co-expressed mRNAs. *CTSS*, *CD180*, and *SCIMP* genes can interact with other co-expressed mRNAs, which were mainly enriched in 50 pathways, such as NF-kB, JAK-STAT, PD-L1 expression & PD-1 checkpoint pathway, and cell adhesion molecules signaling pathways.

ARTICLE HIGHLIGHTS

Research background

Esophageal squamous cell carcinoma (ESCC) is causing a high mortality rate due to the lack of efficient early prognosis markers and suitable therapeutic regimens.

Research motivation

The prognostic role of genes responsible for the acquisition of radioresistance in ESCC has not been fully elucidated.

Research objectives

To establish a prognostic model by studying gene expression patterns pertinent to radioresistance in ESCC patients.

Research methods

Datasets were obtained from the Gene Expression Omnibus and The Cancer Genome Atlas databases. The edgeR, a Bioconductor package, was used to analyze mRNA expression between different groups. We screened genes specifically responsible for radioresistance to estimate overall survival. Pearson correlation analysis was performed to confirm whether the expression of those genes correlated with each other. Genes contributing to radioresistance and overall survival were assessed by the multivariate Cox regression model through the calculation of βi and risk score using the following formula: $\sum_{i=1}^{n} \beta i \times \mathrm{PSI}$.

Research results

We identified three prognostic mRNAs (cathepsin S [*CTSS*], cluster of differentiation 180 [*CD180*], and SLP adapter and CSK-interacting membrane protein [*SCIMP*]) indicative of radioresistance. The

expression of the three identified mRNAs was related to each other ($r > 0.70$ and $P < 0.05$). As to 1-year and 3-year overall survival prediction, the area under the time-dependent receiver operating characteristic curve of the signature consisting of the three mRNAs was 0.716 and 0.841, respectively. When stratifying patients based on the risk score derived from the signature, the high-risk group exhibited a higher death risk and shorter survival time than the low-risk group ($P < 0.0001$). Overall survival of the low-risk patients was significantly better than that of the high-risk patients ($P = 0.018$).

Research conclusions

We have developed a novel three-gene prognostic signature consisting of *CTSS*, *CD180*, and *SCIMO* for ESCC.

Research perspectives

The three-gene signature developed in this study may facilitate the prediction of early prognosis of this malignancy.

FOOTNOTES

Author contributions: Wang XY, Beeraka NM, Xue NN, Yu HM, Yang Y, Liu MX, Nikolenko VN, Liu JQ, and Zhao D conceptualized and designed the study; Beeraka NM, Wang XY, Liu JQ, Zhao D, Xue NN, Yu HM, Nikolenko VN, and Yang Y performed the literature analysis and drafted the manuscript; Beeraka NM, Liu JQ, and Zhao D revised, edited, and extended the final draft; all authors have reviewed and approved the manuscript before submission; Wang XY and Beeraka NM contributed equally to this work.

Institutional review board statement: Since the data of this study were obtained from the TCGA and GEO public databases, in which no personal identification information was included, informed consent was waived by the First Affiliated Hospital of Zhengzhou University.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

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REFERENCES

1 **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**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Wang Y**, Lyu Z, Qin Y, Wang X, Sun L, Zhang Y, Gong L, Wu S, Han S, Tang Y, Jia Y, Kwong DL, Kam N, Guan XY. FOXO1 promotes tumor progression by increased M2 macrophage infiltration in esophageal squamous cell carcinoma. *Theranostics* 2020; **10**: 11535-11548 [PMID: 33052231 DOI: 10.7150/thno.45261]

3 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl ComprCancNetw* 2019; **17**: 855-883 [PMID: 31319389 DOI: 10.6004/jnccn.2019.0033]

4 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

5 **Ohashi S**, Miyamoto S, Kikuchi O, Goto T, Amanuma Y, Muto M. Recent Advances From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma. *Gastroenterology* 2015; **149**: 1700-1715 [PMID: 26376349 DOI:

10.1053/j.gastro.2015.08.054]

6 **Zhan XH**, Jiao JW, Zhang HF, Li CQ, Zhao JM, Liao LD, Wu JY, Wu BL, Wu ZY, Wang SH, Du ZP, Shen JH, Zou HY, Neufeld G, Xu LY, Li EM. A three-gene signature from protein-protein interaction network of LOXL2- and actin-related proteins for esophageal squamous cell carcinoma prognosis. *Cancer Med* 2017; **6**: 1707-1719 [PMID: 28556501 DOI: 10.1002/cam4.1096]

7 **Bayo J**, Tran TA, Wang L, Peña-Llopis S, Das AK, Martinez ED. Jumonji Inhibitors Overcome Radioresistance in Cancer through Changes in H3K4 Methylation at Double-Strand Breaks. *Cell Rep* 2018; **25**: 1040-1050.e5 [PMID: 30355483 DOI: 10.1016/j.celrep.2018.09.081]

8 **Zhou Y**, Chu L, Wang Q, Dai W, Zhang X, Chen J, Li L, Ding P, Zhang L, Gu H, Lv X, Zhang W, Zhou D, Zhang P, Cai G, Zhao K, Hu W. CD59 is a potential biomarker of esophageal squamous cell carcinoma radioresistance by affecting DNA repair. *Cell Death Dis* 2018; **9**: 887 [PMID: 30166523 DOI: 10.1038/s41419-018-0895-0]

9 **Qian D**, Zhang B, Zeng XL, Le Blanc JM, Guo YH, Xue C, Jiang C, Wang HH, Zhao TS, Meng MB, Zhao LJ, Hao JH, Wang P, Xie D, Lu B, Yuan ZY. Inhibition of human positive cofactor 4 radiosensitizes human esophageal squmaous cell carcinoma cells by suppressing XLF-mediated nonhomologous end joining. *Cell Death Dis* 2014; **5**: e1461 [PMID: 25321468 DOI: 10.1038/cddis.2014.416]

10 **Croagh D**, Frede J, Jones PH, Kaur P, Partensky C, Phillips WA. Esophageal stem cells and genetics/epigenetics in esophageal cancer. *Ann N Y AcadSci* 2014; **1325**: 8-14 [PMID: 25266010 DOI: 10.1111/nyas.12521]

11 **He E**, Pan F, Li G, Li J. Fractionated Ionizing Radiation Promotes Epithelial-Mesenchymal Transition in Human Esophageal Cancer Cells through PTEN Deficiency-Mediated Akt Activation. *PLoS One* 2015; **10**: e0126149 [PMID: 26000878 DOI: 10.1371/journal.pone.0126149]

12 **Hein AL**, Ouellette MM, Yan Y. Radiation-induced signaling pathways that promote cancer cell survival (review). *Int J Oncol* 2014; **45**: 1813-1819 [PMID: 25174607 DOI: 10.3892/ijo.2014.2614]

13 **Su H**, Jin X, Zhang X, Zhao L, Lin B, Li L, Fei Z, Shen L, Fang Y, Pan H, Xie C. FH535 increases the radiosensitivity and reverses epithelial-to-mesenchymal transition of radioresistant esophageal cancer cell line KYSE-150R. *J Transl Med* 2015; **13**: 104 [PMID: 25888911 DOI: 10.1186/s12967-015-0464-6]

14 **Zhu H**, Yang X, Ding Y, Liu J, Lu J, Zhan L, Qin Q, Zhang H, Chen X, Yang Y, Liu Z, Yang M, Zhou X, Cheng H, Sun X. Recombinant human endostatin enhances the radioresponse in esophageal squamous cell carcinoma by normalizing tumor vasculature and reducing hypoxia. *Sci Rep* 2015; **5**: 14503 [PMID: 26412785 DOI: 10.1038/srep14503]

15 **Matsuo M**, Matsumoto S, Mitchell JB, Krishna MC, Camphausen K. Magnetic resonance imaging of the tumor microenvironment in radiotherapy: perfusion, hypoxia, and metabolism. *SeminRadiatOncol* 2014; **24**: 210-217 [PMID: 24931096 DOI: 10.1016/j.semradonc.2014.02.002]

16 **Underwood TJ**, Hayden AL, Derouet M, Garcia E, Noble F, White MJ, Thirdborough S, Mead A, Clemons N, Mellone M, Uzoho C, Primrose JN, Blaydes JP, Thomas GJ. Cancer-associated fibroblasts predict poor outcome and promote periostin-dependent invasion in oesophageal adenocarcinoma. *J Pathol* 2015; **235**: 466-477 [PMID: 25345775 DOI: 10.1002/path.4467]

17 **Shigeoka M**, Urakawa N, Nakamura T, Nishio M, Watajima T, Kuroda D, Komori T, Kakeji Y, Semba S, Yokozaki H. Tumor associated macrophage expressing CD204 is associated with tumor aggressiveness of esophageal squamous cell carcinoma. *Cancer Sci* 2013; **104**: 1112-1119 [PMID: 23648122 DOI: 10.1111/cas.12188]

18 **Izawa S**, Mimura K, Watanabe M, Maruyama T, Kawaguchi Y, Fujii H, Kono K. Increased prevalence of tumor-infiltrating regulatory T cells is closely related to their lower sensitivity to H2O2-induced apoptosis in gastric and esophageal cancer. *Cancer ImmunolImmunother* 2013; **62**: 161-170 [PMID: 22865268 DOI: 10.1007/s00262-012-1327-0]

19 **Maher SG**, Gillham CM, Duggan SP, Smyth PC, Miller N, Muldoon C, O'Byrne KJ, Sheils OM, Hollywood D, Reynolds JV. Gene expression analysis of diagnostic biopsies predicts pathological response to neoadjuvant chemoradiotherapy of esophageal cancer. *Ann Surg* 2009; **250**: 729-737 [PMID: 19801928 DOI: 10.1097/SLA.0b013e3181bce7e1]

20 **Park M**, Yoon HJ, Kang MC, Kwon J, Lee HW. PTK7 regulates radioresistance through nuclear factor-kappa B in esophageal squamous cell carcinoma. *TumourBiol* 2016; **37**: 14217-14224 [PMID: 27557627 DOI: 10.1007/s13277-016-5288-3]

21 **Wu H**, Yu J, Kong D, Xu Y, Zhang Z, Shui J, Li Z, Luo H, Wang K. Population and singlecell transcriptome analyses reveal diverse transcriptional changes associated with radioresistance in esophageal squamous cell carcinoma. *Int J Oncol* 2019; **55**: 1237-1248 [PMID: 31638164 DOI: 10.3892/ijo.2019.4897]

22 **Sjoquist KM**, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V; Australasian Gastro-Intestinal Trials Group. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectableoesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; **12**: 681-692 [PMID: 21684205 DOI: 10.1016/S1470-2045(11)70142-5]

23 **Ding M**, Zhang E, He R, Wang X. Newly developed strategies for improving sensitivity to radiation by targeting signal pathways in cancer therapy. *Cancer Sci* 2013; **104**: 1401-1410 [PMID: 23930697 DOI: 10.1111/cas.12252]

24 **Zhao H**, Jiang A, Yu M, Bao H. Identification of biomarkers correlated with diagnosis and prognosis of endometrial cancer using bioinformatics analysis. *J Cell Biochem* 2020 [PMID: 32692884 DOI: 10.1002/jcb.29819]

25 **Zhang H**, Hua Y, Jiang Z, Yue J, Shi M, Zhen X, Zhang X, Yang L, Zhou R, Wu S. Cancer-associated Fibroblast-promoted LncRNA*DNM3OS* Confers Radioresistance by Regulating DNA Damage Response in Esophageal Squamous Cell Carcinoma. *Clin Cancer Res* 2019; **25**: 1989-2000 [PMID: 30463848 DOI: 10.1158/1078-0432.CCR-18-0773]

26 **Ma H**, Zheng S, Zhang X, Gong T, Lv X, Fu S, Zhang S, Yin X, Hao J, Shan C, Huang S. High mobility group box 1 promotes radioresistance in esophageal squamous cell carcinoma cell lines by modulating autophagy. *Cell Death Dis* 2019; **10**: 136 [PMID: 30755598 DOI: 10.1038/s41419-019-1355-1]

27 **Yang L**, Zhang X, Hou Q, Huang M, Zhang H, Jiang Z, Yue J, Wu S. Single-cell RNA-seq of esophageal squamous cell carcinoma cell line with fractionated irradiation reveals radioresistant gene expression patterns. *BMC Genomics* 2019; **20**: 611 [PMID: 31345182 DOI: 10.1186/s12864-019-5970-0]

28 **Yoshino K**, Motoyama S, Koyota S, Shibuya K, Sato Y, Sasaki T, Wakita A, Saito H, Minamiya Y, Sugiyama T, Ogawa J. Identification of insulin-like growth factor 2 mRNA-binding protein 3 as a radioresistance factor in squamous esophageal cancer cells. *Dis Esophagus* 2014; **27**: 479-484 [PMID: 22989274 DOI: 10.1111/j.1442-2050.2012.01415.x]

29 **Pan F**, Mao H, Bu F, Tong X, Li J, Zhang S, Liu X, Wang L, Wu L, Chen R, Wei H, Li B, Li C, Yang Y, Steer CJ, Zhao J, Guo Y. Sp1-mediated transcriptional activation of miR-205 promotes radioresistance in esophageal squamous cell carcinoma. *Oncotarget* 2017; **8**: 5735-5752 [PMID: 27974696 DOI: 10.18632/oncotarget.13902]

30 **Zhu H**, Song H, Chen G, Yang X, Liu J, Ge Y, Lu J, Qin Q, Zhang C, Xu L, Di X, Cai J, Ma J, Zhang S, Sun X. eEF2K promotes progression and radioresistance of esophageal squamous cell carcinoma. *RadiotherOncol* 2017; **124**: 439-447 [PMID: 28431753 DOI: 10.1016/j.radonc.2017.04.001]

31 **Subramanian J**, Simon R. What should physicians look for in evaluating prognostic gene-expression signatures? *Nat Rev ClinOncol* 2010; **7**: 327-334 [PMID: 20421890 DOI: 10.1038/nrclinonc.2010.60]

32 **Seo HR**, Bae S, Lee YS. Radiation-induced cathepsin S is involved in radioresistance. *Int J Cancer* 2009; **124**: 1794-1801 [PMID: 19101991 DOI: 10.1002/ijc.24095]

33 **Hsin MC**, Hsieh YH, Wang PH, Ko JL, Hsin IL, Yang SF. Hispolon suppresses metastasis *via* autophagic degradation of cathepsin S in cervical cancer cells. *Cell Death Dis* 2017; **8**: e3089 [PMID: 28981104 DOI: 10.1038/cddis.2017.459]

34 **Gautam J**, Bae YK, Kim JA. Up-regulation of cathepsin S expression by HSP90 and 5-HT_7 receptor-dependent serotonin signaling correlates with triple negativity of human breast cancer. *Breast Cancer Res Treat* 2017; **161**: 29-40 [PMID: 27796714 DOI: 10.1007/s10549-016-4027-1]

35 **Chen KL**, Chang WS, Cheung CH, Lin CC, Huang CC, Yang YN, Kuo CP, Kuo CC, Chang YH, Liu KJ, Wu CM, Chang JY. Targeting cathepsin S induces tumor cell autophagy *via* the EGFR-ERK signaling pathway. *Cancer Lett* 2012; **317**: 89-98 [PMID: 22101325 DOI: 10.1016/j.canlet.2011.11.015]

36 **Chaplin JW**, Kasahara S, Clark EA, Ledbetter JA. Anti-CD180 (RP105) activates B cells to rapidly produce polyclonal Ig *via* a T cell and MyD88-independent pathway. *J Immunol* 2011; **187**: 4199-4209 [PMID: 21918197 DOI: 10.4049/jimmunol.1100198]

37 **Luo L**, Bokil NJ, Wall AA, Kapetanovic R, Lansdaal NM, Marceline F, Burgess BJ, Tong SJ, Guo Z, Alexandrov K, Ross IL, Hibbs ML, Stow JL, Sweet MJ. SCIMP is a transmembrane non-TIR TLR adaptor that promotes proinflammatory cytokine production from macrophages. *Nat Commun* 2017; **8**: 14133 [PMID: 28098138 DOI: 10.1038/ncomms14133]

38 **Grottke A**, Ewald F, Lange T, Nörz D, Herzberger C, Bach J, Grabinski N, Gräser L, Höppner F, Nashan B, Schumacher U, Jücker M. Downregulation of AKT3 Increases Migration and Metastasis in Triple Negative Breast Cancer Cells by Upregulating S100A4. *PLoS One* 2016; **11**: e0146370 [PMID: 26741489 DOI: 10.1371/journal.pone.0146370]

39 **Park SY**, Lee CJ, Choi JH, Kim JH, Kim JW, Kim JY, Nam JS. The JAK2/STAT3/CCND2 Axis promotes colorectal Cancer stem cell persistence and radioresistance. *J ExpClin Cancer Res* 2019; **38**: 399 [PMID: 31511084 DOI: 10.1186/s13046-019-1405-7]

40 **Hou Y**, Liang H, Rao E, Zheng W, Huang X, Deng L, Zhang Y, Yu X, Xu M, Mauceri H, Arina A, Weichselbaum RR, Fu YX. Non-canonical NF-κB Antagonizes STING Sensor-Mediated DNA Sensing in Radiotherapy. *Immunity* 2018; **49**: 490-503.e4 [PMID: 30170810 DOI: 10.1016/j.immuni.2018.07.008]

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ORIGINAL ARTICLE

Basic Study

5-mRNA-based prognostic signature of survival in lung adenocarcinoma

Qian-Lin Xia, Xiao-Meng He, Yan Ma, Qiu-Yue Li, Yu-Zhen Du, Jin Wang

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Abstract

BACKGROUND

Lung adenocarcinoma (LUAD) is the most common non-small-cell lung cancer, with a high incidence and a poor prognosis.

AIM

To construct effective predictive models to evaluate the prognosis of LUAD patients.

METHODS

In this study, we thoroughly mined LUAD genomic data from the Gene Expression Omnibus (GEO) (GSE43458, GSE32863, and GSE27262) and the Cancer Genome Atlas (TCGA) datasets, including 698 LUAD and 172 healthy (or adjacent normal) lung tissue samples. Univariate regression and LASSO regression analyses were used to screen differentially expressed genes (DEGs) related to patient prognosis, and multivariate Cox regression analysis was applied to establish the risk score equation and construct the survival prognosis model. Receiver operating characteristic curve and Kaplan-Meier survival analyses with clinically independent prognostic parameters were performed to verify the predictive power of the model and further establish a prognostic nomogram.

RESULTS

A total of 380 DEGs were identified in LUAD tissues through GEO and TCGA datasets, and 5 DEGs (TCN1, CENPF, MAOB, CRTAC1 and PLEK2) were screened out by multivariate Cox regression analysis, indicating that the prognostic risk model could be used as an independent prognostic factor (Hazard ratio = 1.520, $P < 0.001$). Internal and external validation of the model confirmed that the prediction model had good sensitivity and specificity (Area under the

curve = 0.754, 0.737). Combining genetic models and clinical prognostic factors, nomograms can also predict overall survival more effectively.

CONCLUSION

A 5-mRNA-based model was constructed to predict the prognosis of lung adenocarcinoma, which may provide clinicians with reliable prognostic assessment tools and help clinical treatment decisions.

Key Words: Lung adenocarcinoma; Differentially expressed genes; Prognostic signature; Risk score; Nomogram

Core Tip: Five differentially expressed genes (DEGs) (TCN1, CENPF, MAOB, CRTAC1, and PLEK2) selected by multiple Cox regression analysis in the prognostic risk models could be considered as independent prognostic factors for lung adenocarcinoma.

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INTRODUCTION

Lung adenocarcinoma (LUAD) is a common histological type of lung cancer that is a malignant tumor that seriously threatens human health, accounting for approximately 40% of lung cancers[1]. In recent years, some progress has been made in diagnostic and treatment strategies of clinical and experimental oncology for lung cancer. However, LUAD patients with localized or locally advanced disease still have a high risk of death, and their 5-year overall survival rate is still less than 15%[2]. Assessing the patient's prognosis can help choose effective treatments to balance side effects with treatment benefits and decide whether to give more aggressive treatment. Although tumor–node–metastasis (TNM) classification plays an important role in the prognosis assessment of LUAD patients, the prognosis of some patients is significantly different even if the stages are similar. Therefore, the identification of reliable prognostic biomarkers to predict clinical outcomes and help make accurate clinical treatment decisions is clearly critical. The rapid development of gene chips and high-throughput sequencing have facilitated the development of new predictive tools based on prognostic genes for lung cancer. These relevant studies involved in prognostic genes of lung cancer have identified several prognostic models that have predicted the overall survival rate of LUAD patients (Table 1)[3-14]. For example, a six-gene model (RRAGB, RSPH9, RPS6KL1, RXFP1, RTL1 and RRM2) based on the weighted gene coexpression network predicted the overall survival rate of non-small-cell lung cancer patients[13]. A 3-gene prognostic model (URKA, CDC20, and TPX2A) also accurately predicted overall survival in smoking-related lung adenocarcinoma[14]. In addition, through analysis of TCGA data, the risk score of the 12-mRNA signature was correlated with poor prognosis in patients with lung adenocarcinoma[3]. Therefore, the in-depth exploration of public databases such as the Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA) databases, discovery of other genes related to the prognosis of LUAD and development of a comprehensive prognosis assessment system including multiple biomarkers may be effective ways to predict the prognosis of lung adenocarcinoma and individual treatment.

Here, we first integrated three lung adenocarcinoma datasets from the GEO database to screen for differentially expressed genes (DEGs). Then, the TCGA-LUAD data set was used to identify DEGs. Univariate Cox and LASSO regression analyses were further used to determine the DEGs associated with overall survival. The risk score was calculated by multiplying multiple Cox coefficients by gene expression. The prognostic model was also combined with clinical parameters to construct a prognostic nomogram to predict overall survival. Finally, Gene set enrichment analysis (GSEA) was performed to identify the potential biological pathways of the five genes in the model.

Table 1 Data and studies involved several prediction models for the prognostic signature of non-small cell lung cancer/ lung adenocarcinoma

Datasets	Model-related genes	Application	Ref.
GEO (GSE19188, GSE33532)	DLGAP5, KIF11, RAD51AP1, CCNB1, AURKA, CDC6, OIP5, NCAPG	Prognostic signature for predicting overall survival in lung adenocarcinoma	Li *et al*[3], 2018
GEO (GSE31210, GSE37745, GSE50081) + TCGA	PLEKHH2, ISCU, CLUL1, CHRDL1, PAIP2B, CDCP1	Prognostic signature for predicting both disease-free and overall survival in non-small cell lung cancer	Zuo *et al*[4], 2019
GEO (GSE31210, GSE37745, GSE50081) + TCGA	CDCP1, HMMR, TPX2, CIRBP, HLF, KBTBD7, SEC24B-AS1, SH2B1	Prognostic Signature for predicting overall survival of early-stage non-small cell lung cancer	He *et al*[5], 2019
TCGA	RHOV, CD109, LINC00941, FRRS1	Prognostic signature for predicting overall survival in lung adenocarcinoma	Shukla *et al*[6], 2016
GEO (GSE3141, GSE30219, GSE50081) + TCGA	ADAM12, BTK, ERG	Prognostic gene signature associated with the microenvironment of lung adenocarcinoma	Yue *et al*[7], 2019
GEO (GSE50081, GSE30219, GSE31210, GSE19188, GSE37745, GSE3141, GSE31908)	ABCC4, ADRBK2, KLHL23, PDS5A, UHRF1, ZNF551	Prognostic signature for predicting overall survival in non-small cell lung cancer	Huang *et al*[8], 2016
GEO (GSE50081, GSE31210, GSE30219, GSE29013, GSE68465, GSE42127) + E-MTAB-923	STAT1, CLU, GTSE1, NUSAP1, ABCA8, TNNT1, ENTPD3, CPA3	Prognostic signature for predicting overall survival in non-small cell lung cancer	Shahid *et al*[9], 2016
GEO (GSE8894, GSE14814, GSE30219, GSE31210, GSE37745, GSE50081)	KIF15, DLGAP5, ASPM, ADAM10, RAD51AP1, FGFR10P, NCGAP	Prognostic gene expression signature for early stage lung adenocarcinoma	Krzystanek *et al* [10], 2016
TCGA	BCHE, CCNA1, CYP24A1, DEPTOR, MASP2, MGLL, MYO1A, PODXL2, RAPGEF3, SGK2, TNNI2, ZBTB16	Prognostic signature for predicting overall survival in lung adenocarcinoma	Zengin *et al* [11], 2020
TCGA	PTPRH, OGFRP1, LDHA, AL365203.1, LINC02178, AL512488.1, LINC01312, AL353746.1, DRAXINP1, LINC02310	Prognostic signature for predicting overall survival in lung adenocarcinoma	Li *et al*[12], 2018
14 GEO datasets	ABCC4, ADRBK2, KLHL23, PDS5A, UHRF1, ZNF551	Prognostic signature for predicting overall survival in non-small cell lung cancer	Xie *et al*[13], 2019
GEO (GSE31210, GSE32863, GSE40791, GSE43458, GSE75037) + TCGA	AURKA, CDC20, TPX2	Prognostic signature for predicting overall survival in smoking-related lung adenocarcinoma	Zhang *et al*[14], 2019

GEO: the Gene Expression Omnibus; TCGA: the Cancer Genome Atlas.

MATERIALS AND METHODS

Gene expression profile data collection from the GEO and TCGA databases

The GEO database (https://www.ncbi.nlm.nih.gov/geo/) was used for the mRNA expression and clinical data of lung adenocarcinoma that needed to meet the following criteria: (1) Human lung adenocarcinoma tissue samples; (2) tumor and nontumor lung control tissue samples; and (3) ≥ 50 samples. Finally, three gene expression microarray data sets (GSE43458, GSE32863 and GSE27262), which included 163 LUAD tumor tissue samples and 113 adjacent normal tissue samples, were downloaded for DEG analysis. On the other hand, the original count data and corresponding clinical data of LUAD patients in the training set and test set, which includes 535 LUAD patient samples and 59 control samples, were downloaded from TCGA project (https://tcga-data.nci.nih.gov/tcga/). Complete survival information and gene expression profile data of 494 patients were obtained from the TCGA database after excluding samples that could not be assessed for tumor histological grade or had no overall survival (OS) information. The model was validated using transcriptome analysis of 90 LUAD patients from the GSE11969 dataset. The workflow of our LUAD biomarker analysis process is shown in Supplementary Figure 1.

Screening and verification of DEGs in lung adenocarcinoma tissue

To identify DEGs between LUAD and lung tissues, GE02R was used for differential expression analysis of the GSE43458, GSE32863, and GSE27262 data sets. The DEGs of the TCGA-LUAD dataset were analyzed using the "limma" software package of R software, and the threshold of DEG screening was $|\log FC| > 2$ and $P < 0.05$ according to our previous study[15]. Human protein mapping (https://www.proteinatlas.org/) evaluates lung adenocarcinoma and DEG protein expression in normal lung tissue[16]. Mutation data in lung adenocarcinoma patients were obtained from cBioPortal (

https://www.cbioportal.org/)[17].

Identification of prognostic differential genes and establishment of prognostic models

TCGA-LUAD data were randomly divided into a training set (n = 346) and a test set (n = 148). In the test set, we performed univariate Cox regression analysis for DEGs determined by a comprehensive analysis of the GEO data set to determine the relationship between patient survival and gene expression. $P < 0.01$ was considered statistically significant and was included in subsequent analysis. Next, we applied LASSO regression to further reduce the number of DEGs in the selected panel with the best predictive performance by 10-fold cross-validation of the R-based glmnet package. Finally, multivariate Cox regression analysis was performed to obtain the five optimal prognostic gene regression coefficients from the multivariate Cox proportional hazard regression model. A prognostic risk score for the five genes was then established based on the multivariate Cox regression model regression coefficient multiplied by a linear combination of its mRNA expression level.

Identification of prognostic models and related genes

The Lung Adenocarcinoma (TCGA, PanCancer Atlas) database in cBioPortal was used to analyze the genetic mutation model. We used data from the TCGA to analyze model-related gene expression. The THPA (http://www.proteinatlas.org) database was used to analyze the protein expression of model-related genes[16]. Patients in the training set were divided into high-risk and low-risk groups according to the median risk score as the cutoff point. Kaplan-Meier (KM) survival curves and Wilcoxon tests combined with the R package "survival" were used to compare the survival differences between the high-risk and low-risk groups. Time-dependent receiver operating characteristic (ROC) curve analysis was conducted using the R software package "survivalROC" to assess the prediction model's forecasting capacity. $P < 0.05$ was considered statistically significant. The test cohort and the entire cohort were used for internal validation, the GSE11969 dataset was downloaded from the GEO database for external validation, and the risk score of each patient was calculated using the same model based on the prognostic gene signature to further verify the predictive value of the prognostic gene signature.

Establish and verify the forecast nomograms

To provide clinicians with a quantitative method for predicting 1-year, 3-year, and 5-year overall survival in LUAD patients, we used a combined model of all independent prognostic factors selected by multivariate Cox regression analysis to construct a nomogram. KM analysis, area under the curve (AUC), consistency index (C-index), and comparison of predicted and observed overall survival were used to evaluate the prognostic nomographs' performance[18].

Functional enrichment analysis of model genes

GSEA was used to analyze the signaling pathways of relevant genes involved in the development of lung adenocarcinoma to clarify the molecular mechanism of the prognostic gene signature. GSEA software (GSEA 4.0.3) was downloaded from the Broad Institute website (http://software.broadinstitute.org/gsea/index.jsp), and the analyzed access was from the c2.cp.kegg.v7.0.symbols.gmt data set in the Molecular Signature Database (MsigDB). The enrichment analysis was carried out by the weighted enrichment method, and the number of random combinations was set as 1000. All other parameters were set as default values. Gene sets with $P < 0.05$ were regarded as significantly enriched gene sets.

Statistical analysis

Statistical analysis and corresponding graph drawing were performed using R3.6.3 software, and Cox regression analysis of the hazard ratio (HR) and 95% confidence interval (CI) was used to evaluate the association between DEG expression and prognosis. A t-test of paired samples or a nonparametric Wilcoxon rank sum test of unpaired samples was used for analysis of continuous variables, and categorical variables were tested by the chi-square test or Fisher's exact test. $P < 0.05$ indicated a significant difference.

RESULTS

Screening and identification of differentially expressed genes in the TCGA-LUAD database

We researched the results as described in the flowchart (Supplementary Figure 1). This study analyzed three GEO datasets (GSE43458, GSE32863, and GSE27262), and 886, 1270, and 1921 DEGs were found, respectively. Then, we found 380 common DEGs by Venn diagram analysis. DEGs were verified in the TCGA-LUAD database (535 Lung adenocarcinoma tissues and 59 Lung cancer tissues), further confirming the differential expression of these 380 genes in lung adenocarcinoma and normal lung tissues (Figure 1A-D).

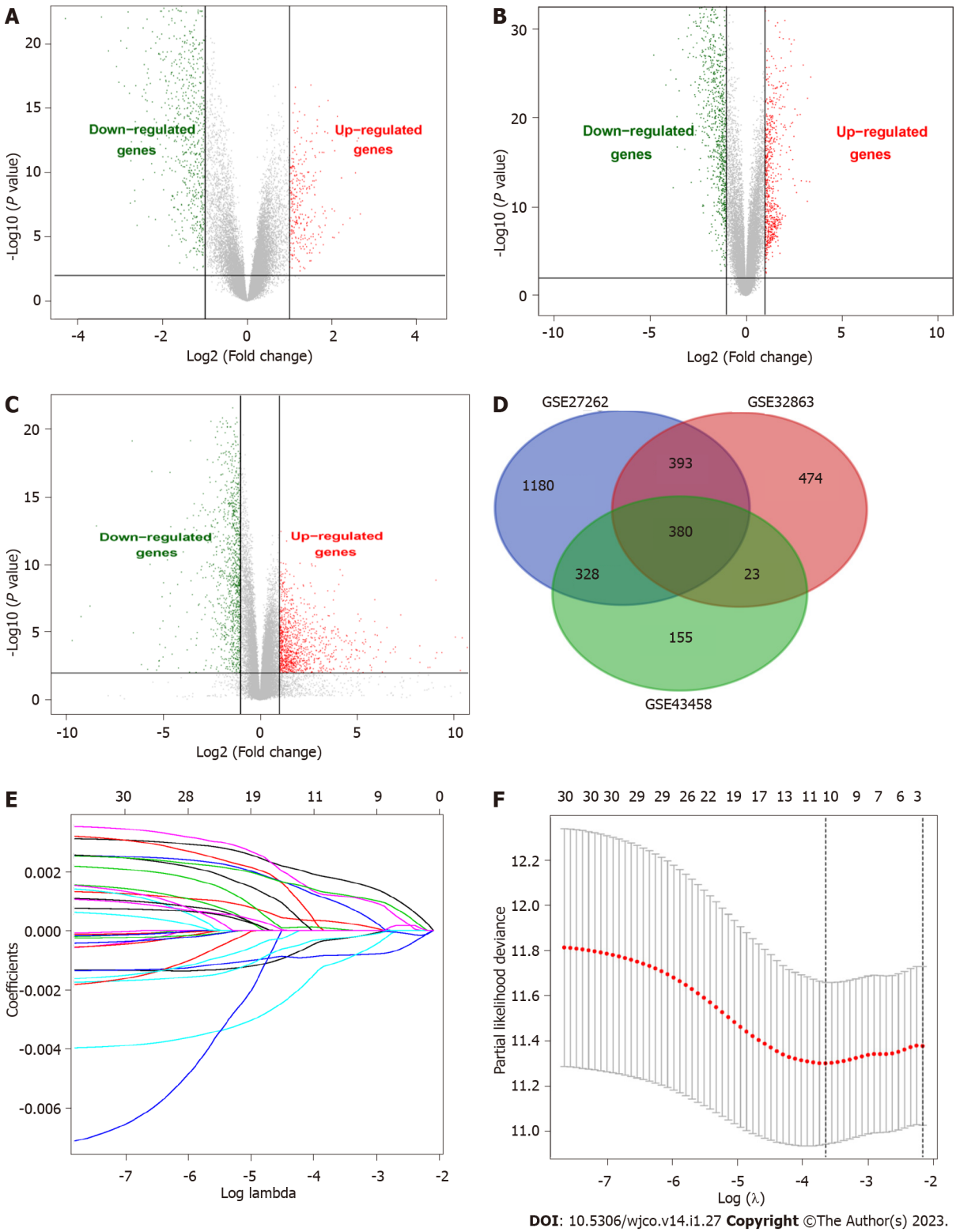

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Figure 1 Screening of differential genes and establishing LASSO regression. A: Volcano map of the differential genes in the GSE43458; B: Volcano map of the differential genes in the GSE32863; C: Volcano map of the differential genes in the GSE27262; D: Venn diagram of the three Gene Expression Omnibus datasets; E: LASSO coefficients profiles of 380 common differential genes; F: LASSO regression with ten- fold cross-validation constructed the models.

Screening of prognostic differential genes and establishment of prognostic models

Univariate Cox regression analysis was performed on 380 DEGs in the training set. A total of 30 DEGs were related to the survival of patients with lung adenocarcinoma ($P < 0.05$) and further screened by LASSO regression (Figure 1E). Cross-validation was used to establish the model, as shown in Figure 1F. A total of 5 mRNAs (TCN1, CENPF, MAOB, CRTAC1, and PLEK2) were included in the model. Multivariate Cox regression analysis was performed for the above 5 mRNAs, and the risk scoring equation was established according to the corresponding regression coefficient. Risk score (RS) =

(0.00288* TCN1 EXP) + (0.0387* CENPF EXP) + (-0.0291* MAOB EXP) + (-0.0198 *CRTAC1 EXP) + (0.0214* PLEK2 EXP).

Verification of mRNA expression and genetic changes associated with 5 prognostic genes

Among the 566 patients included in the cBioPortal for Lung Adenocarcinoma (TCGA, PanCancer Atlas) database, 93 patients (16.4%) showed genetic changes in these 5 genes, among which missense mutations were the most common mutation type (Figure 2A). In the TCGA LUAD cohort, the mRNA expression levels of TCN1, CENPF, and PLEK2 were significantly increased in lung adenocarcinoma tissues compared with those in normal lung tissues, while MAOB and CRTAC1 were significantly decreased in lung adenocarcinoma tissues (Figure 2B). A human protein mapping database (http://www.proteinatlas.org) was used to explore the protein expression level. Immunohistochemical (IHC) results of four genes (TCN1 was not included in the database) in lung cancer and normal lung gland tissues are shown in Figure 2C. Consistent with the mRNA results, IHC results showed that CENPF and PLEK2 had significantly higher mean expression levels in lung adenocarcinoma tissue than in normal lung tissue. In contrast, the CRTAC1 expression level was higher in normal lung tissue than in lung adenocarcinoma tissue. MAOB showed no difference between normal and lung adenocarcinoma tissues (Figure 2C).

Evaluation of five-mRNA prognostic model

Each patient's risk score in the training group was calculated based on the above risk score function. The "SurvMiner" R software package was used to obtain the median critical point, and the patients were divided into a high-risk group and a low-risk group (Figure 3A). As the RS score increased, the patients' survival time was shortened, and the number of deaths increased significantly (Figure 3B). Figure 3C shows the heatmap of 5 prognostic genes in the high- and low-risk groups. The KM survival curve indicated a lower overall survival in the high-risk group than in the low-risk group ($P < 0.001$) (Figure 3D). To further verify the prognostic assessment model's accuracy, we used the R "survival ROC" package to draw the ROC curve (Figure 3E). The results showed that the AUC values of the risk score model for predicting the overall survival at 1, 3 and 5 years in patients with lung adenocarcinoma were 0.711, 0.668 and 0.728, respectively, indicating that the multigene model had a good predictive ability for the OS of patients with lung adenocarcinoma. Multiple Cox regression analysis showed that RS, along with patient age and stage, could be independent prognostic factors for lung adenocarcinoma patients (Figure 3F).

Internal and external validation of the five-mRNA prognostic signature

To verify the predictive value of the 5-mRNA prognostic signature, we used the same formula to calculate risk scores for patients with the internal validation set ($n = 160$), entire validation set ($n = 535$), and external validation set (GSE11969, $n = 90$). Consistent with the training group results, the OS of LUAD patients in the high-risk group was significantly lower than that in the low-risk group (Figure 4A-C). The KM survival analysis of the prognostic signature showed that the AUC values of the 1-year, 3-year, and 5-year OS of the internal validation set, the overall validation set and external validation set were 0.754, 0.630, 0.684, and 0.737, 0.701, 0.680, and 0.779, 0.752, 0.715, respectively (Figure 4D-F). Taken together, our results suggest that this 5-gene signature performs well in predicting overall survival in patients with lung adenocarcinoma.

Establish and verify the nomogram

To establish clinically applicable methods for predicting survival in patients with lung adenocarcinoma, we established a nomogram using three independent prognostic factors (including age, stage, and risk score) to predict 1-year, 3-year, and 5-year OS in patients with lung adenocarcinoma (Supplementary Figure 2A). The calibration diagram showed that the nomogram performs well (Supplementary Figure 2B). The AUC values of the 1-year, 2-year, and 3-year overall survival predictions of the nomograph were 0.760, 0.712, and 0.709, respectively (Supplementary Figure 3A). The KM chart effectively distinguishes the various risks of these categories, with people with higher scores having significantly poorer overall survival ($P < 0.001$) (Supplementary Figure 3B). The C-index (95%CI) of the age, stage, and risk score and combination models was 0.501 (0.480-0.522), 0.684 (0.662-0.076), 0.625 (0.604-0.646), and 0.726 (0.702-0.750), respectively (Supplementary Table 1). Thus, the nomogram performs well in predicting overall survival in patients with lung adenocarcinoma, which may be useful for patient counseling and clinical decision-making.

Biological pathways of the five prognostic model genes were identified

GSEA was performed to identify the potential biological processes of the 5 prognostic genes and showed that the samples with highly expressed TCN1, CENPF, and PLEK2 were enriched with focal adhesion, the p53 signaling pathway, and Toll-like sensors, respectively. MAOB and CRTAC1 samples were mediated in the cell cycle and ubiquitin-mediated proteolysis (Supplementary Figure 4), respectively.

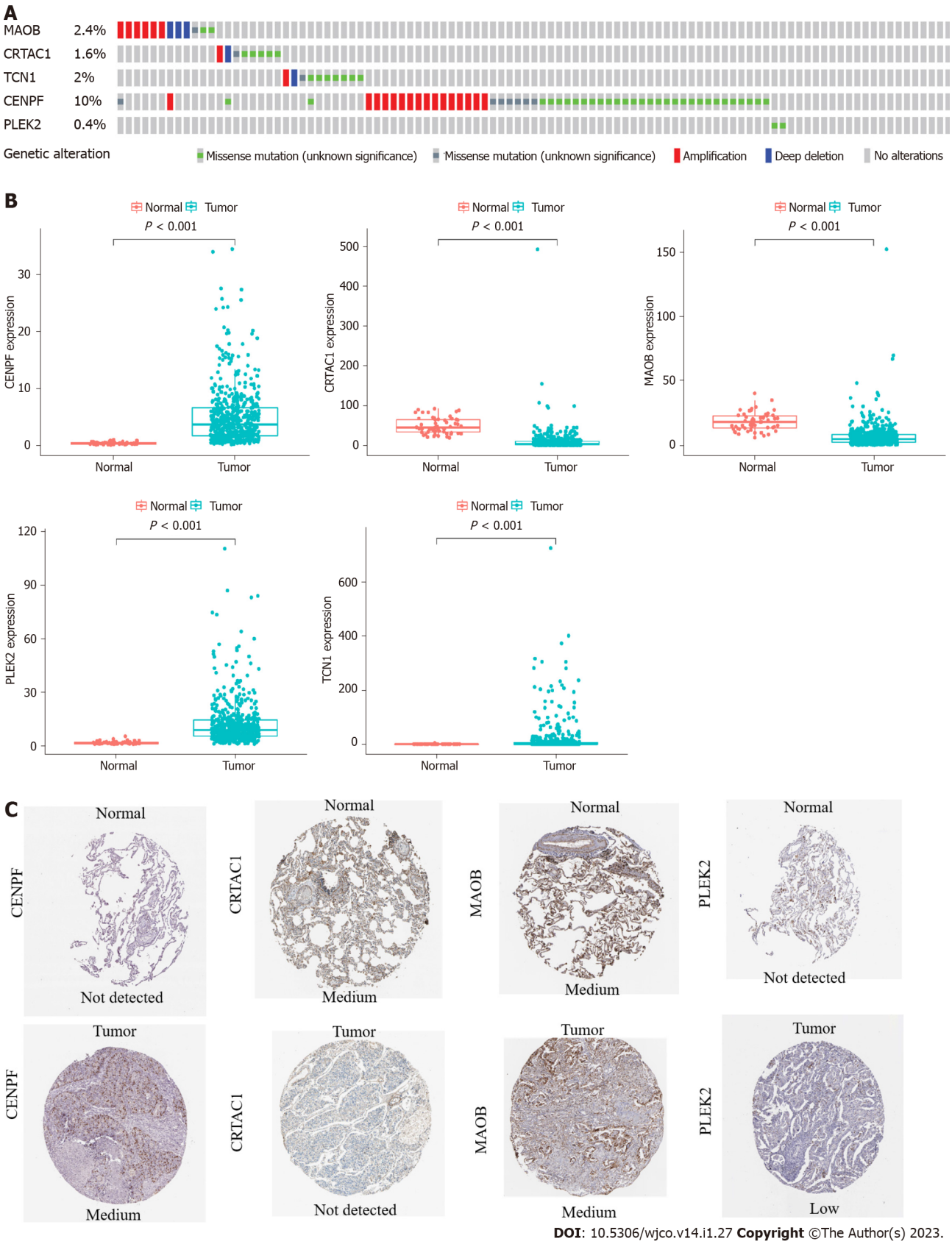

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Figure 2 The expression and genetic alterations of the 5 prognostic genes in Lung adenocarcinoma. A: Genetic alterations rate of 5 model genes; B: Differential expression of the mRNA levels in lung adenocarcinoma tissues; C: Differential expression at the protein levels of the five model genes.

DISCUSSION

Recently, the tumor prognosis model based on the abnormal gene mRNAs has shown great potential due to its high prediction accuracy. Traditional clinicopathological parameters, such as tumor stage,

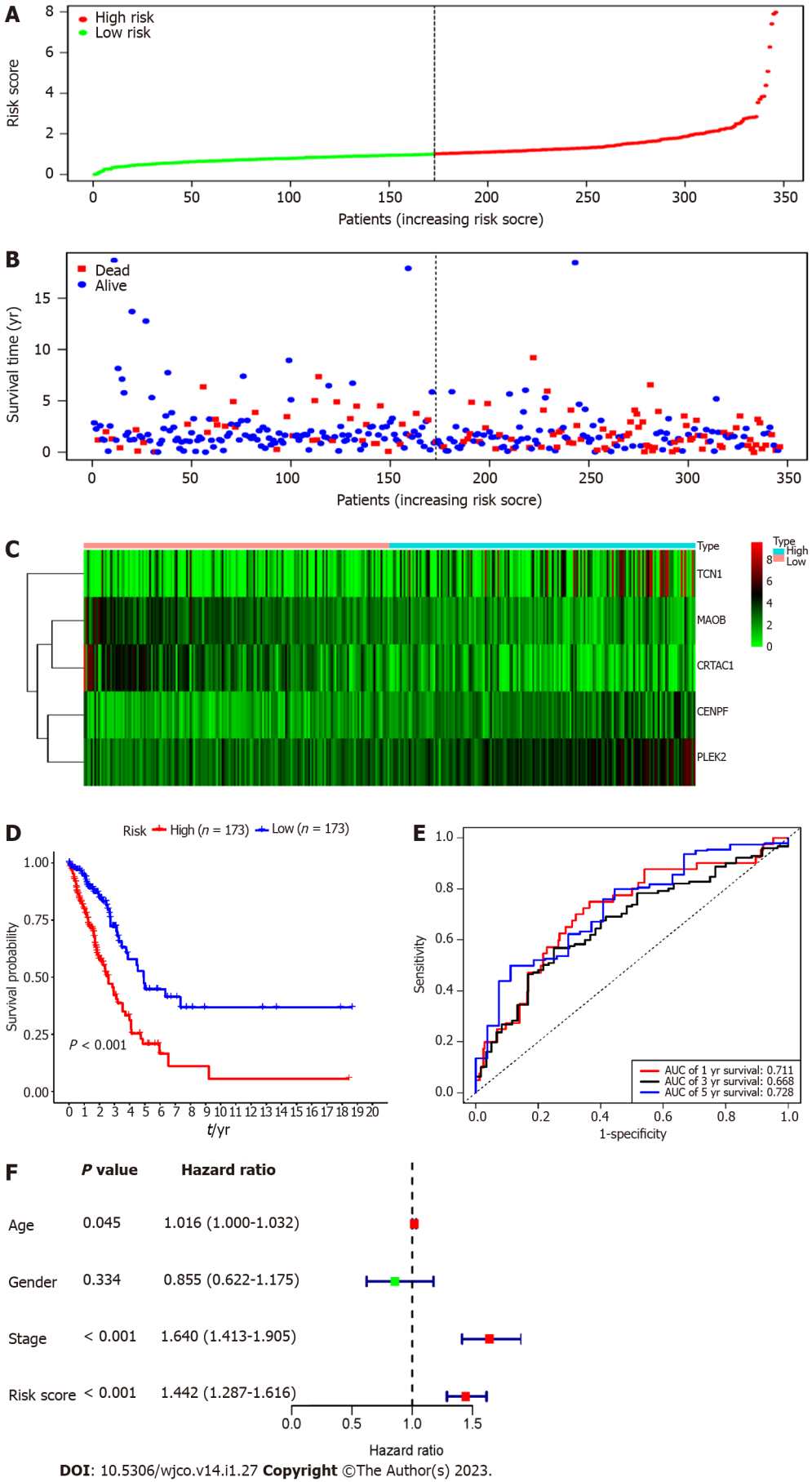

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Figure 3 Risk score model, time-dependent receiver operating characteristic analysis, and survival analysis for the 5-gene signature in

Lung adenocarcinoma. A: The risk score curve divided the patients into the high-risk and low-risk groups; B: Distribution map of the patient's survival status; C: Heatmap of model genes in high and low risk groups; D: Kaplan-Meier survival analysis of the 5-mRNA-based prognostic signature; E: Receiver operating characteristic curves to evaluate the prognostic signature; F: Multiple cox regression analysis of the risk scores and clinical parameters.

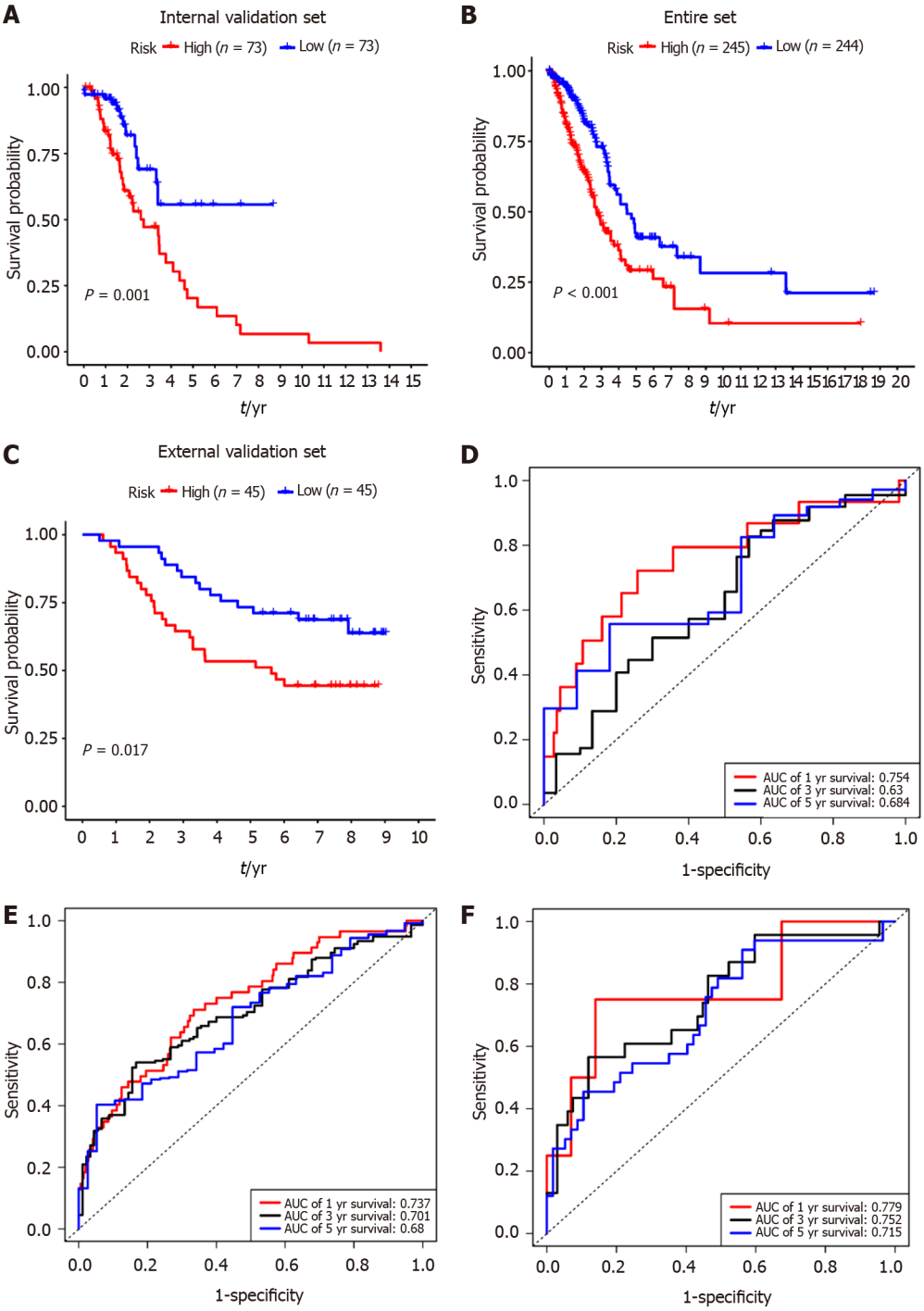

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Figure 4 Internal and external validation of the 5-gene prognostic signature. A: Internal validation by survival analysis; B: The entire dataset validation by survival analysis; C: GSE11969-based external validation by survival analysis; D: Internal validation by receiver operating characteristic (ROC) curves; E: The entire dataset validation by ROC curves; F: GSE11969-based external validation by ROC curves.

have been used to reflect and predict disease progression. However, a single clinical parameter has poor predictive ability for prognosis[3,6,7,10]. In this study, we identified 380 reliable lung adenocarcinoma differential genes by comprehensive analysis of three GEO datasets combined with data from the TCGA-LUAD. Univariate, LASSO and multivariate Cox analyses of DEGs were performed to establish a

prognostic risk model for lung adenocarcinoma based on 5 mRNAs (TCN1, CENPF, MAOB, CRTAC1, and PLEK2). These five new genes were significantly correlated with the prognosis of LUAD patients. MAOB and CRTAC1 were negative prognostic genes, while TCN1, CENPF and PLEK2 were positive prognostic genes. Recently, several studies have revealed the important role of these five genes in cancer progression. Monoamine oxidase B (MAOB) is an enzyme located on the outer mitochondrial membrane. It is responsible for catalyzing monoamine oxidation to produce hydrogen peroxide and is mainly involved in the metabolism of neurotransmitters[19]. The relationship between MAOB and tumors is less reported. It has been reported that MAOB mRNA is significantly lower in the saliva of oral squamous cell carcinoma patients than in that of healthy controls[20]. Xu *et al*[21] found that MAOB is a key DNA methylation driver gene for prostate cancer and plays an important role in the DNA methylation of prostate cancer patients through a comprehensive analysis of the TCGA methylation data. There is no previous report about MAOB in lung adenocarcinoma. CRTAC1 encodes human chondrogenic acid protein 1, which can be used as a marker of chondrocytes to distinguish human chondrocytes from osteoblasts and mesenchymal stem cells in cultures[22]. Currently, this gene is rarely reported in tumors. TCN1 is a member of the vitamin B12-binding protein family and is a 60-70 kDa molecular weight protein. High levels of TCN1 are primarily related to abnormal granulocyte proliferation. TCN1 is overexpressed in a variety of malignancies, such as pancreas, breast, and colon cancer, and is associated with tumor progression and metastasis[23-25]. TCN1 was significantly associated with advanced colorectal cancer[24] and laryngeal cancer[26]. Centromere protein F (CENPF), as an important member of the centromere protein family, is a component of the centromere complex and plays an important regulatory role in mitosis[27]. CENPF expression is abnormally increased in a variety of malignant tumors and is associated with the prognosis of patients[28,29]. Using bioinformatics and immunohistochemical analysis, CENPF overexpression was associated with poor prognosis of breast cancer and tumor bone metastasis[30]. Through comprehensive analysis of three GEO databases, CENPF was identified as a key gene with prognostic value in lung adenocarcinoma, which was consistent with our research results[31]. Pleckstrin-2 (PLEK2) is a 353 amino acid protein encoded by the PLEK2 gene in the human genome and is widely expressed in various tissues. Its overexpression contributes to the formation of large apolipoproteins, thereby promoting cell proliferation[32]. PLEK2 has been found to be related to the invasion and metastasis of multiple tumors. In gallbladder cancer (GBC), PLEK2 overexpression enhances the epithelial-mesenchymal transformation (EMT) process in GBC cells, leading to subsequent higher rates of cell migration, invasion, and liver metastasis[33]. The overexpression of PLEK2 also significantly promoted the EMT and migration of non-small cell lung cancer and destroyed the vascular endothelial barrier[34]. After identifying the five prognostic gene markers, we also conducted internal and external validation to confirm their predictive value and revealed that the prognostic signatures had good prognostic diagnostic value. To improve the prognostic predictive power of the five prognostic gene markers, a predictive nomogram combining risk scores and conventional clinical prognostic parameters (including age and tumor stage) was constructed to enable clinicians to determine the prognosis of each patient. Its graphical scoring system is easy to understand and helps customize treatment and medical decisions. The prognostic models and nomograms associated with five-gene characteristics have not been reported. Hence, our study may be useful prognostic and diagnostic classification tools for lung adenocarcinoma. Our study still has some limitations. First, the study only focuses on transcriptome sequencing data. If other omics techniques, such as DNA methylation and single nucleotide polymorphisms, can be analyzed together, more favorable results may be obtained. Second, our research is limited to the bioinformatics analysis of the TCGA and GEO databases. Although we have verified the accuracy of the models internally and externally, the verification of large samples in the clinical diagnosis and treatment process will further enhance their diagnostic accuracy and clinical value.

CONCLUSION

In summary, our study identified a 5-gene model and prognostic nomogram that combined gene models and clinical prognostic factors to predict the overall survival rate of lung adenocarcinoma patients, and this nomogram may be of great significance for the selection of personalized treatment options and clinical medical decisions in patients with lung adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

Lung adenocarcinoma patients with localized or locally advanced disease have a high risk of death, and their 5-year overall survival rate is less than 15%.

Research motivation

To evaluate the prognosis of Lung adenocarcinoma (LUAD) patients and optimize treatment, effective clinical research prediction models.

Research objectives

To identify reliable prognostic biomarkers to predict clinical outcomes and to help clinicians to make accurate clinical treatment decisions.

Research methods

The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) were used to screen for differential genes for lung adenocarcinoma. Univariate regression analysis combined with LASSO regression analysis was used to screen for prognostic-related genes. Multivariate Cox regression analysis was applied to establish the risk score equation and construct the survival prognosis model.

Research results

We establish a prognostic risk model for lung adenocarcinoma based on 5 mRNAs (TCN1, CENPF, MAOB, CRTAC1, and PLEK2). These five new genes were significantly correlated with the prognosis of LUAD patients. To improve the prognostic predictive power of the five prognostic gene markers, a predictive nomogram combining risk scores and conventional clinical prognostic parameters (including age and tumor stage) was constructed to enable clinicians to determine the prognosis of each patient.

Research conclusions

A 5-mRNA-based model was constructed to predict the prognosis of lung adenocarcinoma, which may provide clinicians with reliable prognostic assessment tools and help clinical treatment decisions.

Research perspectives

Our study identified a 5-gene model and constructed a nomogram which may have important implications for clinical medical decision and personalized treatment of patients with lung adenocarcinoma.

FOOTNOTES

Author contributions: Wang J, Du YZ, and Xia QL conceived and designed the experiments; Xia QL, He XM and Ma Y analyzed the data; Li QY contributed to analysis tools; Xia QL wrote the manuscript; Wang J and Xia QL revised the manuscript; all authors have read and approved the final manuscript.

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Institutional review board statement: The study was reviewed and approved by the Shanghai Public Health Clinical Center Laboratory Animal Welfare & Ethics Committee Institutional Review Board [(Approval No. 2020-A006-01]).

Conflict-of-interest statement: All the authors declare no competing financial interests.

Data sharing statement: The mRNA expression and clinical data of lung adenocarcinoma analyzed during the current study are available on the GEO (https://www.ncbi.nlm.nih.gov/geo/) and TCGA databases (https://www.cbioportal.org/). The protein expression of model-related genes of LUAD analyzed in this study is also available on the THPA database (http://www.proteinatlas.org).

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REFERENCES

1 **Meng W**, Ye Z, Cui R, Perry J, Dedousi-Huebner V, Huebner A, Wang Y, Li B, Volinia S, Nakanishi H, Kim T, Suh SS, Ayers LW, Ross P, Croce CM, Chakravarti A, Jin VX, Lautenschlaeger T. MicroRNA-31 predicts the presence of lymph node metastases and survival in patients with lung adenocarcinoma. *Clin Cancer Res* 2013; **19**: 5423-5433 [PMID: 23946296 DOI: 10.1158/1078-0432.CCR-13-0320]

2 **Drosten M**, Barbacid M. Modeling K-Ras-driven lung adenocarcinoma in mice: preclinical validation of therapeutic targets. *J Mol Med (Berl)* 2016; **94**: 121-135 [PMID: 26526121 DOI: 10.1007/s00109-015-1360-5]

3 **Li S**, Xuan Y, Gao B, Sun X, Miao S, Lu T, Wang Y, Jiao W. Identification of an eight-gene prognostic signature for lung adenocarcinoma. *Cancer Manag Res* 2018; **10**: 3383-3392 [PMID: 30237740 DOI: 10.2147/CMAR.S173941]

4 **Zuo S**, Wei M, Zhang H, Chen A, Wu J, Wei J, Dong J. A robust six-gene prognostic signature for prediction of both disease-free and overall survival in non-small cell lung cancer. *J Transl Med* 2019; **17**: 152 [PMID: 31088477 DOI: 10.1186/s12967-019-1899-y]

5 **He R**, Zuo S. A Robust 8-Gene Prognostic Signature for Early-Stage Non-small Cell Lung Cancer. *Front Oncol* 2019; **9**: 693 [PMID: 31417870 DOI: 10.3389/fonc.2019.00693]

6 **Shukla S**, Evans JR, Malik R, Feng FY, Dhanasekaran SM, Cao X, Chen G, Beer DG, Jiang H, Chinnaiyan AM. Development of a RNA-Seq Based Prognostic Signature in Lung Adenocarcinoma. *J Natl Cancer Inst* 2017; **109** [PMID: 27707839 DOI: 10.1093/jnci/djw200]

7 **Yue C**, Ma H, Zhou Y. Identification of prognostic gene signature associated with microenvironment of lung adenocarcinoma. *PeerJ* 2019; **7**: e8128 [PMID: 31803536 DOI: 10.7717/peerj.8128]

8 **Huang P**, Cheng CL, Chang YH, Liu CH, Hsu YC, Chen JS, Chang GC, Ho BC, Su KY, Chen HY, Yu SL. Molecular gene signature and prognosis of non-small cell lung cancer. *Oncotarget* 2016; **7**: 51898-51907 [PMID: 27437769 DOI: 10.18632/oncotarget.10622]

9 **Shahid M**, Choi TG, Nguyen MN, Matondo A, Jo YH, Yoo JY, Nguyen NN, Yun HR, Kim J, Akter S, Kang I, Ha J, Maeng CH, Kim SY, Lee JS, Kim SS. An 8-gene signature for prediction of prognosis and chemoresponse in non-small cell lung cancer. *Oncotarget* 2016; **7**: 86561-86572 [PMID: 27863408 DOI: 10.18632/oncotarget.13357]

10 **Krzystanek M**, Moldvay J, Szüts D, Szallasi Z, Eklund AC. A robust prognostic gene expression signature for early stage lung adenocarcinoma. *Biomark Res* 2016; **4**: 4 [PMID: 26900477 DOI: 10.1186/s40364-016-0058-3]

11 **Zengin T**, Önal-Süzek T. Analysis of genomic and transcriptomic variations as prognostic signature for lung adenocarcinoma. BMC bioinformatics 2020, 21(Suppl 14):368[DOI: 10.1186/s12859-020-03691-3].

12 **Li YY**, Yang C, Zhou P, Zhang S, Yao Y, Li D. Genome-scale analysis to identify prognostic markers and predict the survival of lung adenocarcinoma. *J Cell Biochem* 2018; **119**: 8909-8921 [PMID: 30105759 DOI: 10.1002/jcb.27144]

13 **Xie H**, Xie C. A Six-Gene Signature Predicts Survival of Adenocarcinoma Type of Non-Small-Cell Lung Cancer Patients: A Comprehensive Study Based on Integrated Analysis and Weighted Gene Coexpression Network. *Biomed Res Int* 2019; **2019**: 4250613 [PMID: 31886214 DOI: 10.1155/2019/4250613]

14 **Zhang MY**, Liu XX, Li H, Li R, Liu X, Qu YQ. Elevated mRNA Levels of AURKA, CDC20 and TPX2 are associated with poor prognosis of smoking related lung adenocarcinoma using bioinformatics analysis. *Int J Med Sci* 2018; **15**: 1676-1685 [PMID: 30588191 DOI: 10.7150/ijms.28728]

15 **Xia Q**, Li Z, Zheng J, Zhang X, Di Y, Ding J, Yu D, Yan L, Shen L, Yan D, Jia N, Chen W, Feng Y, Wang J. Identification of novel biomarkers for hepatocellular carcinoma using transcriptome analysis. *J Cell Physiol* 2019; **234**: 4851-4863 [PMID: 30272824 DOI: 10.1002/jcp.27283]

16 **Thul PJ**, Lindskog C. The human protein atlas: A spatial map of the human proteome. *Protein Sci* 2018; **27**: 233-244 [PMID: 28940711 DOI: 10.1002/pro.3307]

17 **Huang JT**, Wang J, Srivastava V, Sen S, Liu SM. MicroRNA Machinery Genes as Novel Biomarkers for Cancer. *Front Oncol* 2014; **4**: 113 [PMID: 24904827 DOI: 10.3389/fonc.2014.00113]

18 **Li Z**, Chen Z, Hu G, Zhang Y, Feng Y, Jiang Y, Wang J. Profiling and integrated analysis of differentially expressed circRNAs as novel biomarkers for breast cancer. *J Cell Physiol* 2020; **235**: 7945-7959 [PMID: 31943203 DOI: 10.1002/jcp.29449]

19 **Edmondson DE**. Hydrogen peroxide produced by mitochondrial monoamine oxidase catalysis: biological implications. *Curr Pharm Des* 2014; **20**: 155-160 [PMID: 23701542 DOI: 10.2174/13816128113190990406]

20 **Oh SY**, Kang SM, Kang SH, Lee HJ, Kwon TG, Kim JW, Lee ST, Choi SY, Hong SH. Potential Salivary mRNA Biomarkers for Early Detection of Oral Cancer. *J Clin Med* 2020; **9** [PMID: 31963366 DOI: 10.3390/jcm9010243]

21 **Xu N**, Wu YP, Ke ZB, Liang YC, Cai H, Su WT, Tao X, Chen SH, Zheng QS, Wei Y, Xue XY. Identification of key DNA methylation-driven genes in prostate adenocarcinoma: an integrative analysis of TCGA methylation data. *J Transl Med* 2019; **17**: 311 [PMID: 31533842 DOI: 10.1186/s12967-019-2065-2]

22 **Steck E**, Bräun J, Pelttari K, Kadel S, Kalbacher H, Richter W. Chondrocyte secreted CRTAC1: a glycosylated extracellular matrix molecule of human articular cartilage. *Matrix Biol* 2007; **26**: 30-41 [PMID: 17074475 DOI: 10.1016/j.matbio.2006.09.006]

23 **Chong LY**, Cheok PY, Tan WJ, Thike AA, Allen G, Ang MK, Ooi AS, Tan P, Teh BT, Tan PH. Keratin 15, transcobalamin I and homeobox gene Hox-B13 expression in breast phyllodes tumors: novel markers in biological classification. *Breast Cancer Res Treat* 2012; **132**: 143-151 [PMID: 21574054 DOI: 10.1007/s10549-011-1555-6]

24 **Chu CM**, Yao CT, Chang YT, Chou HL, Chou YC, Chen KH, Terng HJ, Huang CS, Lee CC, Su SL, Liu YC, Lin FG, Wetter T, Chang CW. Gene expression profiling of colorectal tumors and normal mucosa by microarrays meta-analysis using prediction analysis of microarray, artificial neural network, classification, and regression trees. *Dis Markers* 2014; **2014**: 634123 [PMID: 24959000 DOI: 10.1155/2014/634123]

25 **Wu Y**, Wei J, Ming Y, Chen Z, Yu J, Mao R, Chen H, Zhou G, Fan Y. Orchestrating a biomarker panel with lncRNAs and mRNAs for predicting survival in pancreatic ductal adenocarcinoma. *J Cell Biochem* 2018; **119**: 7696-7706 [PMID: 29923223 DOI: 10.1002/jcb.27119]

26 **Wang Y**, Yue C, Fang J, Gong L, Lian M, Wang R, Feng L, Ma H, Ma Z, Liu H. Transcobalamin I: a novel prognostic biomarker of neoadjuvant chemotherapy in locally advanced hypopharyngeal squamous cell cancers. *Onco Targets Ther* 2018; **11**: 4253-4261 [PMID: 30100732 DOI: 10.2147/OTT.S166514]

27 **Varis A**, Salmela AL, Kallio MJ. Cenp-F (mitosin) is more than a mitotic marker. *Chromosoma* 2006; **115**: 288-295 [PMID: 16565862 DOI: 10.1007/s00412-005-0046-0]

28 **Brendle A**, Brandt A, Johansson R, Enquist K, Hallmans G, Hemminki K, Lenner P, Försti A. Single nucleotide polymorphisms in chromosomal instability genes and risk and clinical outcome of breast cancer: a Swedish prospective case-control study. *Eur J Cancer* 2009; **45**: 435-442 [PMID: 19008095 DOI: 10.1016/j.ejca.2008.10.001]

29 **Chen WB**, Cheng XB, Ding W, Wang YJ, Chen D, Wang JH, Fei RS. Centromere protein F and survivin are associated with high risk and a poor prognosis in colorectal gastrointestinal stromal tumours. *J Clin Pathol* 2011; **64**: 751-755 [PMID: 21613637 DOI: 10.1136/jcp.2011.089631]

30 **Sun J**, Huang J, Lan J, Zhou K, Gao Y, Song Z, Deng Y, Liu L, Dong Y, Liu X. Overexpression of CENPF correlates with poor prognosis and tumor bone metastasis in breast cancer. *Cancer Cell Int* 2019; **19**: 264 [PMID: 31632198 DOI: 10.1186/s12935-019-0986-8]

31 **Song YJ**, Tan J, Gao XH, Wang LX. Integrated analysis reveals key genes with prognostic value in lung adenocarcinoma. *Cancer Manag Res* 2018; **10**: 6097-6108 [PMID: 30538558 DOI: 10.2147/CMAR.S168636]

32 **Hu MH**, Bauman EM, Roll RL, Yeilding N, Abrams CS. Pleckstrin 2, a widely expressed paralog of pleckstrin involved in actin rearrangement. *J Biol Chem* 1999; **274**: 21515-21518 [PMID: 10419454 DOI: 10.1074/jbc.274.31.21515]

33 **Luo Y**, Robinson S, Fujita J, Siconolfi L, Magidson J, Edwards CK, Wassmann K, Storm K, Norris DA, Bankaitis-Davis D, Robinson WA, Fujita M. Transcriptome profiling of whole blood cells identifies PLEK2 and C1QB in human melanoma. *PLoS One* 2011; **6**: e20971 [PMID: 21698244 DOI: 10.1371/journal.pone.0020971]

34 **Wu DM**, Deng SH, Zhou J, Han R, Liu T, Zhang T, Li J, Chen JP, Xu Y. PLEK2 mediates metastasis and vascular invasion *via* the ubiquitin-dependent degradation of SHIP2 in non-small cell lung cancer. *Int J Cancer* 2020; **146**: 2563-2575 [PMID: 31498891 DOI: 10.1002/ijc.32675]

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