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MINIREVIEWS

Oncologic safety of colonic stenting as a bridge to surgery in left-sided malignant colonic obstruction: Current evidence and prospects

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Abstract

Approximately 7%-29% of patients with colorectal cancer present with colonic obstruction. The concept of self-expandable metal stent (SEMS) insertion as a bridge to surgery (BTS) is appealing. However, concerns on colonic stenting possibly impairing oncologic outcomes have been raised. This study aimed to review current evidence on the short- and long-term oncologic outcomes of SEMS insertion as BTS for left-sided malignant colonic obstruction. For short-term outcomes, colonic stenting facilitates a laparoscopic approach, increases the likelihood of primary anastomosis without a stoma, and may decrease postoperative morbidity. However, SEMS-related perforation also increases local recurrence and impairs overall survival. Moreover, colonic stenting may cause negative oncologic outcomes even without perforation. SEMS can induce shear forces on the tumor, leading to increased circulating cancer cells and aggressive pathological characteristics, including perineural and lymphovascular invasion. The conflicting evidence has led to discordant guidelines. Well-designed collaborative studies that integrate both oncologic outcomes and data on basic research (*e.g.*, alteration of circulating tumors) are needed to clarify the actual benefit of colonic stenting as BTS.

Key Words: Bridge to surgery; Colon cancer; Colorectal surgery; Emergency treatment; Intestinal obstruction; Self-expandable metal stent

Core Tip: Although the concept of self-expandable metal stent (SEMS) insertion as a bridge to surgery in patients with left-sided malignant colonic obstruction is promising, there remain concerns of adverse oncologic outcomes. Nowadays, three possible mechanisms of tumor dissemination from SEMS have been proposed: (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement. However, among these, only SEMS-related perforation clearly influences adverse oncologic outcomes. The other two mechanisms lack consistent clinical evidence for their association with decreased survival. Therefore, further collaborating studies are needed to validate the clinical impact of these hypotheses.

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignant disease worldwide, with more than 1.9 million new cases recorded in 2020[1]. Patients with CRC are presented with bowel obstruction for 7%-29%[2]. The outcomes of emergency surgery (ES) for patients with obstructed CRC are worse than those of elective surgery for patients without obstruction. Patients with obstructed CRC also have a higher mortality rate than those without obstruction (17% *vs* 6%, respectively)[3]. The causes of the high morbidity and mortality of ES are advanced-stage cancer, malnutrition, electrolyte abnormalities, colonic mucosa injury from distention, and fecal loading of the obstructed colon[4]. The self-expandable metal stent (SEMS) insertion as a bridge to surgery (BTS) concept, which converts an emergency condition to an elective one, is fascinating. Colonic decompression by SEMS gives time to stabilize medical conditions that distinctly benefit high-risk patients.

The benefits of SEMS as BTS for right-sided malignant colonic obstruction (RMCO, defined as an obstructed tumor located between the cecum and distal transverse colon) are limited. Currently, right colectomy with primary anastomosis is the recommended treatment for RMCO[5]. Ileocolic anastomosis is associated with the lowest incidence of leaks, ranging from 1% to 3%, and can be performed in cases with obstructive situation[6,7]. Therefore, the World Society of ES (WSES) guideline does not recommend SEMS as BTS for RMCO except in high-risk patients[5]. In contrast, SEMS insertion as BTS in left-sided malignant colonic obstruction (LMCO, defined as an obstructed tumor located between the splenic flexure and rectosigmoid junction) is very beneficial. In addition to the feasibility of laparoscopic resection, SEMS insertion allows the feasibility of elective single-stage colonic resection with a lower risk of permanent stoma creation[8].

However, the long-term oncologic outcomes are a matter of concern. SEMS induces shear force to the tumor and may lead to cancer cell dissemination into the peritoneal cavity, lymphatic fluid, and bloodstream[9,10]. A few studies suggested that SEMS insertion was associated with worse oncologic outcomes than ES, especially in patients with SEMS-related perforation[11,12]. Nevertheless, recent studies with low complication rates reported good oncologic outcomes with SEMS placement as BTS[13-19]. As a result, current guidelines are dynamic and discordant because of the conflicting evidence[20-24].

As such, this study aimed to perform a comprehensive review of the current evidence on the short- and long-term oncologic outcomes of SEMS insertion as BTS for LMCO.

TREATMENT OPTIONS FOR LMCO

ES

Emergent procedures for LMCO include various procedures such as Hartmann's procedure, segmental colectomy with/without on-table lavage, and subtotal/total colectomy. These procedures result in high morbidity and mortality because of the limited time to stabilize the patient's condition before surgery [4]. Among these, Hartmann's procedure remains one of the most common emergency procedures for the left colon because of the short operative time and avoidance of anastomotic leakage[25]. However, the rate of reversal of Hartmann's procedure is less than 50% because this operation is associated with high morbidity and possible mortality[26,27]. As a result, most of them turn to permanent stomas that severely affect the patient's quality of life. Laparoscopic approach for ES of LMCO has limited application because of technical difficulties during surgery. The WSES guideline does not recommend its use except in selected cases in specialist centers[5].

Colonic stenting as BTS

Dohmoto *et al*[28] was the first to report the idea of using plastic tubes as colonic stenting for palliation of obstructed rectal cancer in 1991. One year later, Spinelli *et al*[29] started using SEMS insertion as a palliative modality with good results. After the success of palliative SEMS placement, the BTS concept was introduced by Tejero *et al*[30] in 1994. They described 3 phases of SEMS as BTS: (1) Relieving obstruction by SEMS; (2) recovering the patient's condition and mechanically preparing the colon; and (3) definitive elective surgery. It has been 30 years since the introduction of colonic stenting. Palliative SEMS placement is established as a preferred option in incurable malignant colonic obstruction because it confers superior quality of life by avoiding stoma and is associated with shorter time to initiation of chemotherapy than palliative surgery[21]. In contrast, the role of SEMS as BTS is still controversial, with concerns of adverse oncologic outcomes after SEMS insertion limiting its application as BTS.

Stent materials and technical considerations

There are different types of SEMS materials including stainless steel, elgiloy, and nitinol[31]. Endoscopists should be aware of the characteristics of each stent. Stainless steel stents are relatively stiff and interfere with magnetic resonance imaging (MRI) examination. Meanwhile, elgiloy stents have better elasticity and flexibility and do not interfere with MRI assessment. Nitinol stents are made of nickel-titanium and have poorer fluoroscopic visualization compared with elgiloy stents. Therefore, radiopaque markers, such as gold or silver markers, are added to both ends of these stents. Nitinol stents have superior flexibility and better memory to hold the original shape than stainless steel and elgiloy stents; consequently, nitinol stents are popular worldwide.

SEMS is classified as covered or uncovered. Covered SEMS has a silicone membrane on bare wires, preventing tumor ingrowth. For obstructed CRC, uncovered SEMS is recommended for both curative and palliative settings[21]. A recent meta-analysis, including one randomized controlled trial (RCT) and nine observational studies, compared covered and uncovered SEMS in curative and palliative settings. The study found that uncovered SEMS was associated with fewer complications (relative risk [RR]: 0.57; 95%CI: 0.44-0.74; $P < 0.001$), tumor ingrowth (RR: 0.29; 95%CI: 0.09-0.93; $P = 0.040$), and SEMS migration (RR: 0.29; 95%CI: 0.17-0.48; $P < 0.001$)[32]. Meanwhile, there was limited evidence regarding the optimal SEMS diameter[21]. Previous studies showed no association between SEMS diameter and success or perforation rate[33,34]. However, a few studies suggested an association between SEMS diameter < 24 mm and adverse events, especially migration[35-37]. Regarding SEMS length, it is recommended that the SEMS should be long enough to extend at least 1.5-2 cm on each side of the lesion, and the degree of SEMS shortening after deployment must be considered[21].

Colonic stenting can be performed endoscopically (through-the-scope technique) or fluoroscopically (over-the-wire technique). Several studies showed comparable technical success rate between endoscopic and fluoroscopic methods, but a combined endoscopic-fluoroscopic method showed the highest success rate[38-41]. Therefore, the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends that colonic stenting should be performed with the combined use of endoscopy and fluoroscopy[21]. For the combined technique, a soft-tipped hydrophilic guidewire is passed through the strictured lumen. Contrast injection helps to delineate the stenosis and to confirm guidewire placement under fluoroscopy. The SEMS is then passed over the guidewire and deployed under endoscopic visualization and fluoroscopic guidance[42] (Figure 1). Stricture dilation should not be performed either before or after colonic stenting as it increases the risk of perforation[21,43]. The recommended interval to curative resection after BTS stenting is approximately 2 wk[21].

Benefit of colonic stenting as BTS for LMCO

Owing to the high morbidity (45%-50%) and mortality (15%-20%) of ES for obstructed CRC, the BTS concept of avoiding an emergent situation is appealing[44]. After relieving the obstruction by SEMS placement, the clinicians can have time to stabilize the patients, improve their nutrition, correct electrolyte imbalance, and mechanically prepare the colon before definite resection. In addition, it is crucial that surgeons gain the ability to perform laparoscopic resection after BTS stenting (Figure 2). Compared with open resection, laparoscopic resection is associated with lower postoperative pain, earlier recovery of bowel function, and shorter hospital stay[45].

Nine RCTs have investigated the short-term outcomes of SEMS placement as BTS in comparison with those of ES for LMCO (Table 1). Notably, perforation after SEMS insertion and the success rate influenced postoperative outcomes. Four RCTs without perforation showed that SEMS insertion as BTS had a lower morbidity rate than ES[46-49]. Meanwhile, 1 RCT with a low stent success rate (70%) and 3 RCTs with 6.6%-12% perforation rate showed no difference in morbidity between SEMS insertion as BTS and ES[15,50-52]. Additionally, RCTs with low perforation rate also showed a significantly lower rate of postoperative stoma[15,46,53]. Stoma is well recognized to adversely affect quality of life. We conducted meta-analyses that included these nine RCTs. Of these, seven, nine, and seven studies reported the stoma rates, postoperative morbidity, and mortality rates, respectively. In the SEMS group, the stoma rate (RR: 0.68; 95%CI: 0.55-0.85, $I^2 = 19\%$) and postoperative morbidity (RR: 0.67; 95%CI: 0.48-0.94, $I^2 =$

Table 1 Short-term outcomes in randomized controlled trials of colonic stenting as a bridge to surgery

Ref.	Year	*n*	Perforation rate (%)	Stoma rate (%)	Morbidity (%)	Mortality (%)
Cheung *et al*[46]	2009	48	0	SEMS, 0; ES, 25, (P = 0.03)[a]	SEMS, 8; ES, 70; (P = N/A)	N/A
Van Hooft *et al*[51]	2011	98	12	SEMS, 57; ES, 66; (P = 0.35)	SEMS, 53; ES, 45; (P = 0.43)	SEMS, 19; ES, 17; (P = 0.84)
Pirlet *et al*[52]	2011	60	6.6	SEMS, 43; ES, 56; (P = 0.3)	SEMS, 50; ES, 56; (P = 1)	SEMS, 10; ES, 3; (P = N/A)
Alcántara *et al*[47]	2011	28	0	N/A	SEMS, 13; ES, 54; (P = 0.042)[a]	SEMS, 0; ES, 8; (P = 0.46)
Ho *et al*[50]	2012	39	0	SEMS, 10; ES, 31; (P = 0.12)	SEMS, 35; ES, 58; (P = 0.15)	SEMS, 0; ES, 16; (P = 0.1)
Ghazal *et al*[48]	2013	60	0	N/A	SEMS, 13; ES, 50; (P = 0.012)[a]	SEMS, 0; ES, 0
Arezzo *et al*[15]	2017	115	8.9	SEMS, 22; ES, 39; (P = 0.031)[a]	SEMS, 52; ES, 58; (P = 0.529)	SEMS, 7; ES, 5; (P = 0.943)
Elwan *et al*[49]	2020	60[1]	0	SEMS, 20; ES, 27; (P = N/A)	SEMS, 23; ES, 40; (P = 0.029)[a]	N/A
CReST trial[53]	2022	217[2]	3.3[3]	SEMS, 43; ES, 67; (P < 0.001)[a]	SEMS, 34; ES, 35; (P = 0.930)	SEMS, 4; ES, 6; (P = 0.480)

[a]P<0.05

[1]In this study, 85% of patients have left-sided malignant colonic obstruction, and 15% have right-sided malignant colonic obstruction.

[2]There are 217 potentially curative patients from 245 patients.

[3]The rate is reported in all patients (93% patients with potentially curable disease and 7%, palliative disease).

ES: Emergency surgery; SEMS: Self-expandable metal stent; N/A: Not available.

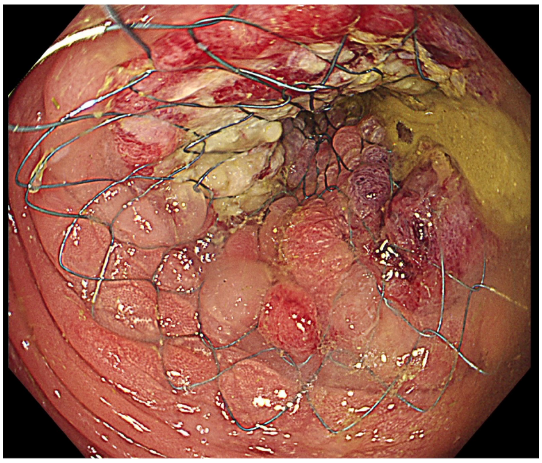

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Figure 1 Endoscopic image of deployed stent.

65%) were significantly lower than those in the ES group (Figures 3 and 4). There were no differences in mortality rates between the SEMS and ES groups (RR: 0.95; 95%CI: 0.53-1.70, I^2 = 0%) (Figure 5).

In 2021, Cirocchi *et al*[54] conducted a systematic review and meta-analysis of RCTs and found that compared with ES, SEMS placement as BTS had a higher rate of successful primary anastomosis (RR: 1.26; 95%CI: 1.01-1.57), lower stoma rate (RR: 0.62; 95%CI: 0.45-0.85), and lower postoperative complication (RR: 0.61; 95%CI: 0.45-0.85). The mortality rate was comparable between the two modalities. To conclude, SEMS placement as BTS clearly has short-term benefits of higher primary anastomosis, lower stoma rate, and lower morbidity than ES. In this context, low perforation and high stenting success rates are needed to benefit from SEMS.

ONCOLOGIC OUTCOMES AFTER COLONIC STENTING IN CURABLE DISEASE

Despite the impressive short-term results of SEMS placement as BTS, its application has been debated due to concerns about adverse long-term oncologic outcomes. Theoretically, shear forces created by SEMS might lead to cancer cell dissemination through the following three possible mechanisms (Figure 6): (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement.

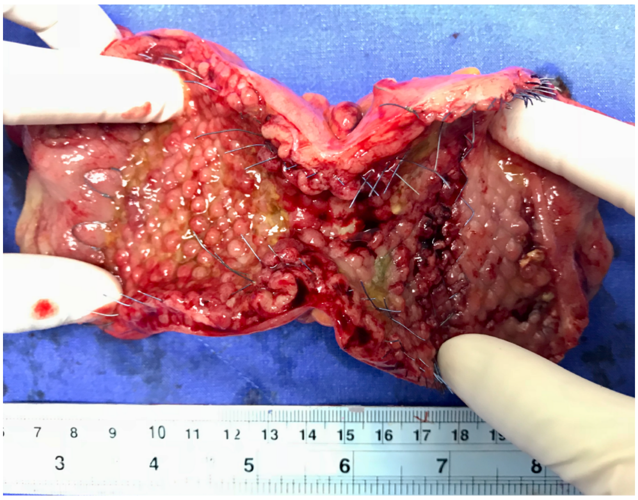

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Figure 2 Surgical specimen after laparoscopic colectomy following colonic stenting as a bridge to surgery.

Study or Subgroup	SEMS Events	SEMS Total	ES Events	ES Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Cheung 2009	0	24	6	24	0.6%	0.08 [0.00, 1.29]	2009
Pirlet 2011	13	30	17	30	14.5%	0.76 [0.46, 1.28]	2011
Van Hooft 2011	27	47	34	51	29.5%	0.86 [0.63, 1.18]	2011
Ho 2012	2	20	6	19	2.1%	0.32 [0.07, 1.38]	2012
Arezzo 2017	11	56	23	59	10.7%	0.50 [0.27, 0.94]	2017
Elwan 2020	6	30	8	30	5.1%	0.75 [0.30, 1.90]	2020
CReST trial 2022	47	110	72	107	37.4%	0.63 [0.49, 0.82]	2022
Total (95% CI)		**317**		**320**	**100.0%**	**0.68 [0.55, 0.85]**	
Total events	106		166				

Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.45, df = 6 (*P* = 0.28); I^2 = 19%
Test for overall effect: Z = 3.42 (*P* = 0.0006)

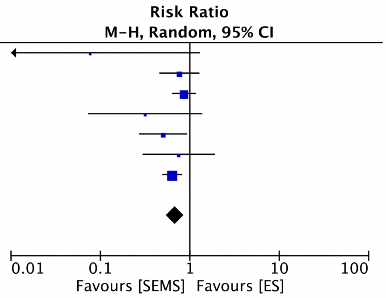

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Figure 3 Forest plot showing the stoma rate. SEMS: Self-expandable metal stent; ES: Emergency surgery.

Study or Subgroup	SEMS Events	SEMS Total	ES Events	ES Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Cheung 2009	2	24	17	24	4.8%	0.12 [0.03, 0.45]	2009
Alcantara 2011	2	15	7	13	4.6%	0.25 [0.06, 0.99]	2011
Pirlet 2011	15	30	17	30	14.4%	0.88 [0.55, 1.42]	2011
Van Hooft 2011	25	47	23	51	15.7%	1.18 [0.79, 1.77]	2011
Ho 2012	7	20	11	19	10.7%	0.60 [0.30, 1.23]	2012
Ghazal 2013	4	30	15	30	7.5%	0.27 [0.10, 0.71]	2013
Arezzo 2017	29	56	34	59	16.9%	0.90 [0.64, 1.26]	2017
Elwan 2020	7	30	12	30	9.7%	0.58 [0.27, 1.28]	2020
CReST trial 2022	33	110	36	107	15.9%	0.89 [0.60, 1.32]	2022
Total (95% CI)		**362**		**363**	**100.0%**	**0.67 [0.48, 0.94]**	
Total events	124		172				

Heterogeneity: Tau^2 = 0.15; Chi^2 = 22.54, df = 8 (*P* = 0.004); I^2 = 65%
Test for overall effect: Z = 2.32 (*P* = 0.02)

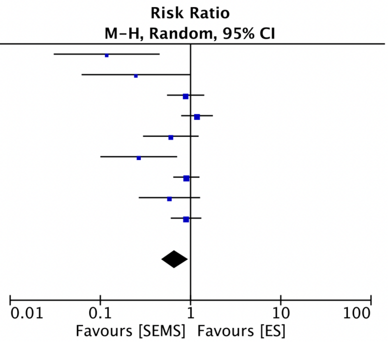

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Figure 4 Forest plot showing the postoperative morbidity rate. SEMS: Self-expandable metal stent; ES: Emergency surgery.

SEMS-related perforation

In obstructed CRC, manipulation of the ulcerated and necrotic tissue through SEMS may cause tumor perforation, which is the most feared complication of SEMS insertion. Perforation causes tumor dissemination into the peritoneal cavity and increases locoregional recurrence and peritoneal carcinomatosis, which affects long-term outcomes[55]. Perforation can be classified into clinical and silent perforation. Interestingly, some studies showed that silent perforation in SEMS as BTS can occur in up to 6%-27% of patients[43,51,52,56]. Further, this rate may still be underestimated because silent perforation can be diagnosed only from pathological assessment of the surgical specimen. Given that there have been sparse reports of silent perforation in the literature, its impact on oncologic outcomes is difficult to

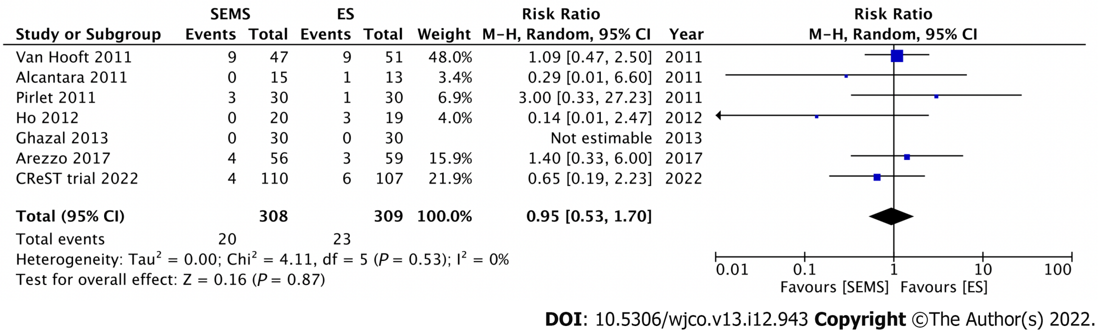


Figure 5 Forest plot showing the overall mortality rate. SEMS: Self-expandable metal stent; ES: Emergency surgery.

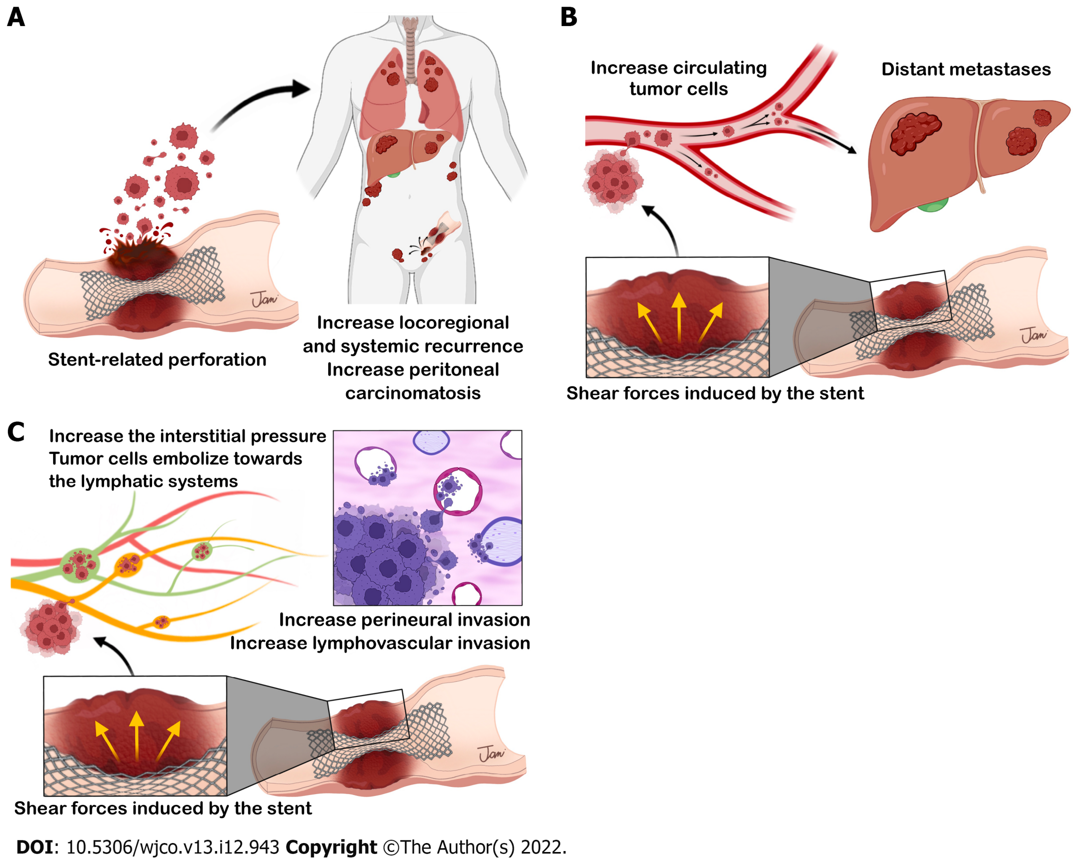


Figure 6 Three possible mechanisms of tumor dissemination after self-expandable metal stent placement. A: self-expandable metal stent (SEMS)-related perforation; B: Increased circulating tumor cells; C: Aggressive pathological features after SEMS placement.

verify; however, it should not be disregarded.

In the Dutch Stent-In 2 trial, Sloothaak *et al*[57] found that 83% of patients with SEMS-related perforation have recurrence. Moreover, Gorissen *et al*[11] suggested that local recurrence was higher in patients who underwent SEMS placement as BTS than in those who underwent ES (32% *vs* 8%, $P = 0.04$). In this study, all patients with perforation had recurrence. Sabbagh *et al*[58] found that SEMS-related perforation was an independent risk factor for poor overall survival. Sensitivity analyses revealed that 3-year overall survival was better in studies with < 8% SEMS-related perforation rate than in those with ≥ 8%[59]. Balciscueta *et al*[55] recently conducted a systematic review and meta-analysis of 13 studies (1 RCT, 4 prospective studies, 8 retrospective studies) with long-term oncologic outcomes. The overall rate of SEMS-related perforation was 8.9%. The locoregional recurrence rate was higher in patients with perforation than in those without perforation (26.6% *vs* 12.5%; OR: 2.41; 95%CI: 1.33-4.34; $P = 0.04$), while the systemic recurrence rate was comparable.

In summary, SEMS-related perforation influences the occurrence of adverse oncologic outcomes; therefore, an endoscopist's experience and expertise are crucial with respect to deciding between SEMS placement as BTS or ES. The ESGE guideline recommends a shared decision-making discussion with the patient that should include the availability of stenting expertise and the risk of perforation in the endoscopy unit[21].

Increased circulating tumor cells

SEMS placement could impair oncologic outcomes despite the absence of perforation. SEMS exerts shear forces on the tumor and makes tumor cells disseminate throughout the body[60]. Maruthachalam *et al*[9] found a more significant rise in cytokeratin 20 messenger RNA expression in peripheral circulation after SEMS placement than after conventional colonoscopy. The presence of messenger RNA coding for epithelial markers indicates the presence of tumor cells or shed debris in the circulation. Furthermore, Yamashita *et al*[10] found that SEMS placement induces tumor cell dissemination into the peripheral circulation. Using circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) as indicators, Takahashi *et al*[61] recently found that SEMS insertion may cause massive cellular and tumor damage. The patients who underwent SEMS placement had higher postoperative plasma levels of both cfDNA and ctDNA than did those who underwent transanal tube decompression. On the contrary, Ishibashi *et al*[62] found that the increase of circulating tumor cells after SEMS insertion may be temporary, as in most cases, the number of circulating tumor cells decreased 4 d after SEMS placement. Although evidence of tumor cell dissemination after SEMS placement exists, there is inadequate clinical evidence of its negative effects on survival and prognosis.

Aggressive pathological features after SEMS placement

SEMS insertion leads to a sudden increase in interstitial pressure inside the tumor mass, possibly causing detachment of cells and tumor embolization towards the lymphatic systems and resulting in lymphatic invasion[63]. Hayashi *et al*[64] noted that the tumor pressure is important, not only for the number of tumor cells shed, but also for the size of emboli shedding into lymphatics around the tumor. Several studies revealed that SEMS insertion might promote perineural invasion found in surgical specimens, although these studies failed to translate higher perineural invasion into poorer oncologic outcomes[18,65-67]. Meanwhile, various studies found that SEMS had no significant effect on the incidence of perineural invasion compared with ES[8,68-70]. Conflicting findings with respect to other adverse pathological features such as lymphovascular and vascular invasion have also been reported [13,18,19,65,67,70-72]; therefore, cumulative data are needed. Balciscueta *et al*[73] recently conducted a meta-analysis of 1273 patients from 10 retrospective cohort studies and found higher perineural invasion (OR: 1.98; 95%CI: 1.22-3.21; P = 0.006) and lymphatic invasion (OR: 1.45; 95%CI: 1.10-1.90; P = 0.008) after SEMS insertion than after ES. Therefore, the use of SEMS as BTS should be carefully considered due to an increase in adverse pathological characteristics, although the long-term adverse oncological effects have not been demonstrated.

Oncologic outcomes of colonic stenting as BTS from RCTs

Six RCTs have reported long-term oncologic outcomes after SEMS placement as BTS compared with those of ES (Table 2). For the studies without SEMS-related perforation, the recurrence and survival outcomes are not significantly different between the two modalities[47,48,74]. In contrast, the Dutch Stent-In 2 trial, which had a high perforation rate of 23%, reported poorer disease-free survival in patients who underwent SEMS insertion as BTS than in those underwent ES[57]. This study underlined the strong association between SEM-related perforation and adverse oncologic outcomes. The long-term follow-up outcomes of the ESCO and CReST trials have been recently published. The ESCO trial reported comparable oncologic outcomes between the two modalities, with an 8.9% rate of SEMS-related perforation rate[75]. Similarly, the CReST trial found a comparable 3-year recurrence rate and overall survival between SEMS as BTS and ES, with a low SEMS-related perforation rate of 3.3%[53]. The latest systematic review and meta-analysis of five RCTs by Cirocchi *et al*[54] revealed comparable recurrence rates and oncologic outcomes between SEMS placement as BTS and ES. We conducted a meta-analysis of these six RCTs that reported the recurrence rate. There was no significant difference in recurrence rates between the SEMS and ES groups (RR: 1.45; 95%CI: 0.96-2.17, I^2 = 45%) (Figure 7).

These clinical studies show that among the three proposed mechanisms of cancer cell dissemination by SEMS, only SEMS-related perforation clearly influences adverse oncologic outcomes. Sensitivity analyses showed that a < 8% perforation rate is the oncologically safe cut-off point for SEMS insertion [59]. Therefore, endoscopy units that aim to perform SEMS as BTS should audit and improve their SEMS-related perforation rate to be lower than 8%. Two other mechanisms, including increased circulating tumor cells and aggressive pathological features, failed to produce consistent clinical evidence in decreased overall and disease-free survival in the SEMS group. Therefore, further studies are needed to validate the clinical impact of these hypotheses.

Table 2 Long-term outcomes in randomized controlled trials of colonic stenting as a bridge to surgery

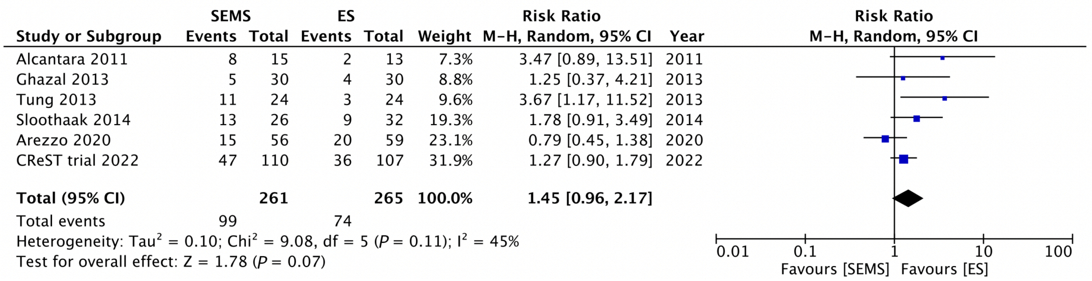
Ref.	Year	*n*	Perforation rate (%)	Median F/U time (mo)	Recurrence (%)	Overall survival (OS, %)	Disease-free survival (DFS, %)
Alcántara *et al*[47]	2011	28	0	38	SEMS, 53; ES, 15; (*P* = 0.055)	5-yr OS: SEMS, 60; ES, 68; (*P* = 0.843)	Disease-free period (mo): SEMS, 25; ES, 27; (*P* = 0.096)
Tung *et al*[74]	2013	48	0	32	SEMS, 46; ES, 13; (*P* = 0.400)	5-yr OS: SEMS, 48; ES, 27; (*P* = 0.076)	5-yr DFS: SEMS, 52; ES, 48; (*P* = 0.630)
Ghazal *et al* [48]	2013	60	0	18	SEMS, 17; ES, 13; (*P* = 0.228)	N/A	N/A
Sloothaak *et al*[57]	2014	58	23	43	SEMS, 50; ES, 28; (*P* = N/A)	4-yr OS: SEMS, 58; ES, 67; (*P* = 0.478)	4-yr DFS: SEMS, 30; ES, 49; (*P* =0.007)[a]
Arezzo *et al* [75]	2020	115	8.9	37	SEMS, 28; ES, 36; (*P* = N/A)	3-yr OS: SEMS, 63; ES, 68; (*P* = 0.822)	3-yr DFS: SEMS, 50; ES, 56; (*P* = 0.972)
CReST trial [53]	2022	217[1]	3.3[2]	N/A	3-yr recurrence: SEMS, 43; ES, 34; (*P* = 0.340)	3-yr OS: SEMS, 46; ES, 37; (*P* = 0.560)	N/A

[a]$P<0.05$

[1]There are 217 potentially curative patients from 245 patients.

[2]The rate is reported in all patients (93% patients with potentially curable disease and 7%, palliative disease).

ES: Emergency surgery; SEMS: Self-expandable metal stent; N/A: Not available.



DOI: 10.5306/wjco.v13.i12.943

Figure 7 Forest plot showing the overall recurrence rate. SEMS: Self-expandable metal stent; ES: Emergency surgery.

CHEMOTHERAPY IN PATIENTS WITH COLONIC STENTS

Neoadjuvant chemotherapy in locally advanced colon cancer

The mainstay treatment of the potentially curable colon cancer is complete oncologic resection. However, one of the challenges is the risk of local and distant recurrence, which is estimated at 20%-30% in locally advanced colon cancer (defined as: T3 tumors with ≥ 5 mm invasion beyond the muscularis propria; T4; or extensive regional lymph node involvement without distant metastases)[76]. Recently, there was increasing evidence to support the use of neoadjuvant chemotherapy in locally advanced colon cancer[77-81]. The theoretical advantages include the early treatment of micrometastases, increased likelihood of clear resection (R0) margin, and ability to evaluate the chemosensitivity of the tumor[76]. Gosavi *et al*[76] conducted a meta-analysis of two RCTs and reported that neoadjuvant chemotherapy increased the likelihood of R0 resection in locally advanced colon cancer (RR 0.47; 95%CI: 0.47-0.96) without an increase in complications (anastomotic leak, wound infection, or re-operation). However, the safety of neoadjuvant chemotherapy after SEMS placement in obstructive colon cancer is also a concern.

There were a few studies using neoadjuvant chemotherapy after SEMS placement in obstructive colon cancer. The FOxTROT trial showed a significant decrease in R1 resection rate in patients who received neoadjuvant chemotherapy for locally advanced colon cancer. However, only a few patients in this trial underwent SEMS placement as BTS; therefore, a conclusion about SEMS safety could not be drawn[79]. Recently, Han *et al*[82] conducted a comparative study investigating the safety of neoadjuvant chemotherapy after SEMS placement. They found that the adverse events of preoperative chemotherapy were well-tolerated, and the neoadjuvant chemotherapy did not increase SEMS-related complications (P = 0.13). Moreover, this study revealed that patients who received neoadjuvant chemotherapy had better overall survival than those who received postoperative chemotherapy (mean overall survival, 53 *vs* 47 mo, respectively, P = 0.02). However, well-designed RCTs with larger sample size and long-term follow-up are needed to confirm the safety and potential survival benefit of neoadjuvant chemotherapy after SEMS placement.

Chemotherapy in patients with incurable stage IV colon cancer

Patients with incurable stage IV colon cancer benefit from SEMS placement by avoiding palliative surgery and early initiation of chemotherapy. However, there is a concern that chemotherapy during SEM placement might induce complications. For palliative SEMS placement, many studies (including patients with and without chemotherapy) reported perforation rates of 7%-13%[83-88]. Therefore, the decision to perform SEM insertion in patients with incurable stage IV colon cancer must consider the risks of long-term SEMS-related complications weighted against SEMS benefits[89].

The administration of antiangiogenic agents (*e.g.*, bevacizumab) in patients who underwent SEMS placement was found to increase the risk of SEMS-related perforation. A retrospective study reported 3-fold higher perforation rate in patients who received bevacizumab after SEMS placement than in those who did not receive bevacizumab[90]. In a large retrospective study of 1008 patients who received bevacizumab for incurable colon cancer, Bong *et al*[91] found that SEMS placement is a significant risk factor for complications requiring surgery in patients who received bevacizumab (HR 5.69, 95%CI 2.37-13.64, $P < 0.001$). In contrast, a retrospective study reported no significant difference in perforation rate in patients who received chemotherapy with and without bevacizumab (7.3% *vs* 7.0%, respectively, $P = 0.925$)[92]. The updated 2020 ESGE guideline recommends chemotherapy as a safe treatment in patients who have undergone palliative SEMS insertion. However, SEMS placement should not be performed while patients are receiving antiangiogenic therapy[21].

FUTURE DIRECTION

Although many RCTs and prospective and retrospective studies have investigated the role of SEMS placement as BTS in comparison with that of ES in LMCO, current evidence is still conflicting, and the international guidelines are also dynamic and discordant[20,21]. In 2014, the ESGE guideline did not recommend using SEMS insertion as BTS based on previous studies with low success and high perforation rates[20]. Nevertheless, many comparative studies and one RCT published thereafter[13-19, 93] reported impressive short- and long-term oncologic outcomes. As such, the updated ESGE guideline released in 2020 considers SEMS placement as BTS a valid treatment option in patients with LMCO. The guideline emphasized that the medical team has to discuss the risks and benefits of SEMS with patients and SEMS insertion should be performed or directly supervised by a competent endoscopist[21].

The proficiency of the endoscopist is crucial when SEMS as BTS is considered. Previous RCTs with low perforation rate showed appreciable short-term outcomes of SEMS, including lower stoma rate, higher primary anastomosis, lower morbidity, and comparable oncologic outcomes to ES[15,46-49,74, 75]. Moreover, current evidence clearly demonstrates the association between SEMS-related perforation and negative oncologic outcomes. Therefore, SEMS placement as BTS is a valid option for competent endoscopists.

Impaired oncological outcomes after SEMS placement that result from increased circulating tumor and adverse pathological characteristics remain a concern. However, current evidence could not demonstrate adverse long-term oncological effects. Further well-designed collaborative studies are needed to investigate the association among the alteration of circulating tumors, adverse pathological characteristics, and oncologic outcomes.

CONCLUSION

Colonic obstruction is a common presentation of CRC that needs emergency intervention. SEMS placement as BTS, converting an emergency situation to an elective one, improves short-term outcomes in LMCO, including higher primary anastomosis, lower stoma rate, and lower postoperative morbidity, compared with ES. However, there remain concerns on adverse oncologic outcomes from shear forces induced by SEMS. There are three possible mechanisms of tumor dissemination from SEMS: (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement. However, among these, only SEM-related perforation clearly influences adverse oncologic outcomes. Consistent clinical evidence supporting the association of the other two mechanisms with decreased overall and disease-free survival is lacking. Therefore, further well-designed collaborative studies are needed to validate the clinical impact of these mechanisms. Current guidelines consider SEMS placement as BTS a valid treatment option in patients with LMCO, but it should be performed by competent endoscopists.

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MINIREVIEWS

Colonic stent for bridge to surgery for acute left-sided malignant colonic obstruction: A review of the literature after 2020

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Abstract

It has been found that 8%-29% of colorectal cancers are obstructive. The use of "stent as bridge to surgery" is one of the most debated topics in obstructive left-sided colorectal cancer management. The endoscopic placement of a self-expanding metallic stent as bridge to surgery (BTS) could turn an emergency surgery to an elective one, increasing the number of primary anastomoses instead of stoma and facilitating the laparoscopic approach instead of an open one. However, in recent years the possible risk of perforations and microperforations facilitating cancer spread related to the use of self-expanding metallic stent for BTS has been highlighted. Therefore, despite the useful short-term outcomes related to BTS, the recent literature has focused on long-term outcomes investigating the disease-free survival, the recurrence rate and the overall survival. Due to discordant data, international guidelines are still conflicting, and the debate is still open. There is not agreement about using self-expanding metallic stent for BTS as the gold standard.

Key Words: Colorectal cancer obstruction; Anastomosis; Laparoscopy; Recurrence rate; Overall survival; Guidelines

Core Tip: The most recent articles (published after 2020) about self-expanding metallic stent as bridge to surgery in left-sided colorectal cancer obstruction were collected. Both the short-term and long-term outcomes were analyzed, focusing on the role of stent-related microperforations in worsening disease-free and overall survival rates. Despite the growing number of studies published in recent years, the use of self-expanding metallic stent as bridge to surgery is not considered the gold standard due to conflicting reports. Updating meta-analyses, randomized studies and reviews will help determine new international guidelines and a shared treatment flow-chart.

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INTRODUCTION

It is known that 8%-29% of colorectal cancers (CRC) are initially characterized by obstruction[1]. In the management of left-sided colonic obstruction there are two different options: emergency surgery (ES) and stent placement as bridge to surgery (BTS). Historically, an ES was first considered for distal malignant obstruction[2]. In this context, three different surgical options could be considered[3]: (1) Three-stage management, in which the first intervention is a proximal stoma formation, followed by colonic resection and stoma reversal; (2) Two-stage management (Hartmann's intervention); and (3) One-stage management that consists of resection and primary anastomosis. About 20 years ago the SEMS placement was first used to decompress neoplastic stenosis[4].

ES is often conducted with an open approach because a distended bowel may hamper laparoscopy [5]. In addition to that, ES frequently concludes with stoma formation that negatively impacts patient quality of life[6]. This is why the interest in BTS has become increasingly important. In fact, authors have primarily focused on short-term outcomes of using SEMS for BTS, such as anastomosis and stoma rate, laparoscopic and open approach and postoperative hospital stay. On the other hand, the recent BTS literature is focused on long-term outcomes, such as disease-free survival (DFS), overall survival (OS) and progression-free survival. Due to the length of time since the start of using SEMS for BTS, a multitude of data have been collected (Figure 1).

However, despite a growing number of articles about CRC obstruction, the use of SEMS for BTS is still debated. No uniform international guidelines have been published yet due to the hypothesized role of microperforations worsening the long-term outcomes of patients. The purpose of this review was to collect the latest (since 2020) research on SEMS for BTS use. In one of the more updated systematic reviews and meta-analyses[7], only two studies published after 2020 were included (Arezzo *et al*[8] multicentric study and Allievi *et al*[9] single center study). Both the international guidelines and the short-term/long-term outcomes focusing on the new data published after 2020 have been analyzed (the "update" part of each chapter).

GUIDELINES

In left-sided colonic obstructions, colonic stenting in a palliative setting is commonly accepted. However, the best treatment in a curative setting is still debated. There is still not agreement whether SEMS placement for BTS or upfront ES is better.

Some of the most important American guidelines recommend stent insertion as the first choice to solve colonic obstruction[10,11], while another considers both possibilities to be equally valid[12]. In general, the attitude of European guidelines is more moderate. No guidelines consider the insertion of a stent as the only option[13-15]. Both approaches are also considered in the World Society of Emergency Surgery[16]. Webster *et al*[17] analyzed high-quality international recommendations published between 2010 and 2019 and found that only two studies considered the use of a stent as the gold standard.

In this context, another discussed point is the "time to elective surgery," which is the time between stent insertion and elective surgery[18,19]. Theoretically a delayed interval between SEMS placement and definitive surgery could allow better recovery and improve nutritional status, but it could be burdened by a high rate of local tumor infiltration and fibrosis[20]. Not all guidelines indicate the ideal number of days between stent positioning and surgery. However, in the American Society for Gastrointestinal Endoscopy 6 d before elective surgery is considered the best interval. After the 6th day the risk of perforation is increased[10]. In the Eastern Association for the Surgery of Trauma an interval of 7 d is considered[21].

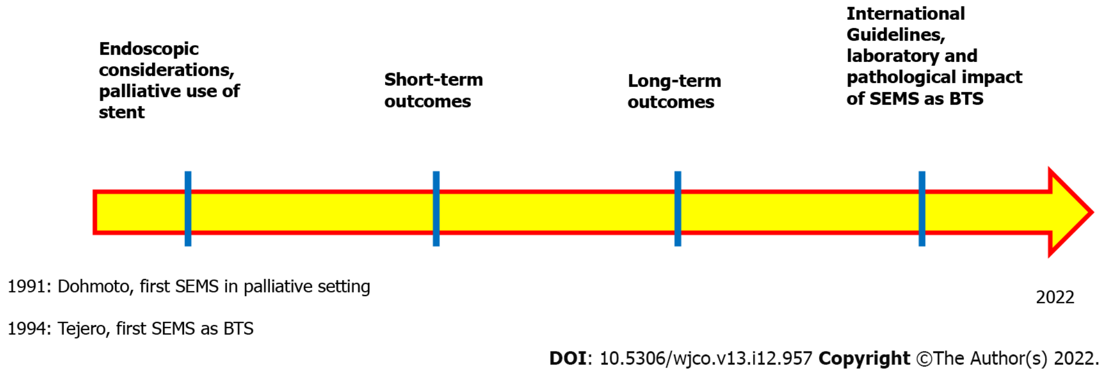

Figure 1 Self-expandable metallic stent as bridge to surgery timeline. Topic of interest of self-expandable metallic stent (SEMS) used as bridge to surgery from the initial use to current use. BTS: Bridge to surgery.

Update

Recently, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines-Update 2020 has been published[22]. They strongly recommend with high quality of evidence that stenting for BTS as an option in patients with potentially curable left-sided obstruction, and it must represent a shared decision-making process. This main recommendation is different from the 2014 ESGE guidelines, which stated that the stent placement could be considered as an alternative only for patients with American Society of Anesthesiologists ≥ III and/or age > 70 years[23]. However, in the 2014 and 2020 editions, the most important recommendation to use SEMS for BTS should be reserved for patients without signs of perforation (always strong recommendation)[22]. In the recent ESGE guidelines a time interval of 2 wk until surgery is considered (weak recommendation, low quality evidence)[22].

ENDOSCOPIC CONSIDERATIONS

For patients suspected of having a neoplastic left-sided colonic obstruction, an urgent colonoscopy is usually performed[24]. It may be useful to identify other colonic lesions and to stage cancer with more accuracy[25].

The SEMS placement remains a challenging procedure. The technical success is defined as the endoscopic correct stent placement, while the clinical success is the resolution of the obstruction[26]. SEMS can be covered and uncovered. The uncovered SEMS can be divided into through-the-scope and non-through-the-scope[27]. The through-the-scope SEMS is inserted through a guidewire. The diameter of the SEMS is about 18-22 mm[24]. In the majority of studies[24,25] the WallFlex enteral colonic stent and the Niti-S enteral colonic stent were used.

SEMS placement for BTS has been extensively studied for left-sided colonic obstruction, while limited data have been collected for the right-sided obstruction[28].

Although severe endoscopic adverse events complicate < 5% of procedures[10], early and late complications can sometimes occur[29]. Some early complications (within 30 d) are migration, perforation and bleeding, while some late complications (after 30 d) are a late obstruction, migration and perforation. The covered SEMS have a higher migration rate and lower obstruction rate, while uncovered SEMS have a lower migration rate[27]. Only a few studies investigated the predictors of technical failures, but it seems that a stenosis > 8 cm may be associated with a higher rate of technical failure[30].

Update

A central part of the updated ESGE guideline is dedicated to endoscopic technical considerations. Colonic stenting should be performed directly or supervised by a medical figure both with colonoscopy and fluoroscopic expertise[22].

In 2021, a multicenter prospective cohort study affirmed that the WallFlex stent was the most used globally[31].

Some authors tried to compare the feasibility and safety of SEMS for BTS based on the grade of colonic neoplastic obstruction, classified 0 to 2 by the Colorectal Obstruction Scoring System. No differences were found in safety and short-term outcomes in patients classified as 0, 1 or 2[26].

An effort to standardize the SEMS placement has been made. It has likely contributed to excellent short-term outcomes, technical success and low perforation rate[31].

According to the most recent literature, colonic stenting should be performed by endoscopists who demonstrate a good expertise as it represent a challenging procedure, In some articles a minimum number of procedures is indicated[32]. If stenting expertise is not available, decompressing stoma as a bridge to elective surgery should be considered[22].

It was shown that delaying surgery can lead to a significantly higher recurrence rate[33].

LABORATORY AND ANATOMOPATHOLOGICAL CONSIDERATIONS

In the last 2-3 years there has been a growing interest about the possible association between SEMS for BTS and worse long-term oncological outcomes, such as perineural invasion (PNI) and vascular and lymphatic invasion[34]. The presence of PNI seems to decrease long-term survival[34]. The PNI negatively impacts recurrence and survival in CRC. In some studies, there was no difference in perineural invasion between the ES group and the SEMS for BTS group[35]. The tumor stage and vascular invasion were found to be independent risk factors for PNI in patients with obstructing colonic stenting[36]. According to Wang *et al*[37], PNI may be associated with obstruction but not with stent insertion.

In other articles, laboratory elements, such as circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA), have been identified. cfDNA, which indicates cellular damage, is derived from apoptotic or necrotic cells. ctDNA indicates tumor-derived DNA possibly from apoptotic or necrotic cells, and it could contain gene mutations. During the endoscopic procedure of colonic stenting the manipulation of the tumor could increase plasma ctDNA and cfDNA[38]. Stent-induced neoplastic manipulation may lead malignant cells to local and distant invasion, worsening long-term outcomes [38].

Broholm *et al*[39] performed a gene expression analysis. The Nano String Counter Pan Cancer Immune Oncology Panel 360 gene expression was used. They observed that SEMS for BTS induced changes in gene expression in the neoplastic microenvironment, related to progression in CRC and may induce a more aggressive phenotype. These changes seemed to be caused by mechanical pressure of the cancer and the following inflammation of tissue. Six genes promoting angiogenesis were significantly upregulated. Tumor-promoting inflammation gene expression, such as *IL-6*, were involved. The use of anti-inflammatory drugs after stenting has been proposed[39].

SHORT-TERM OUTCOMES

In almost all studies postoperative complications are analyzed. Postoperative outcomes such as 30-d or 60-d mortality, anastomosis rate and laparoscopic rate are often considered.

The most important advantages of using a SEMS for BTS is transforming an urgent surgery to an elective one and maintaining bowel continuity by avoiding stoma creation[40,14]. In fact, a primary anastomosis can be created more safely in an elective setting than in an urgent or emergent setting. Wang *et al*[41] revealed in their meta-analysis that the use of colonic stenting could not increase the risk of anastomotic leakage incidence compared with emergency surgery.

Using a stent for BTS approach could be different as well. Donlon *et al*[42] reported a 78% rate of the laparoscopic approach. However, in the same year Boland *et al*[43] reported only three studies (41%) in which the laparoscopic approach was successfully completed after the stent insertion.

According to De Ceglie *et al*[44], postsurgical complications like infections were less frequent in patients undergoing urgent surgery. In the same article, the hospitalization rate was similar in the ES and BTS groups. On the other hand, Consolo *et al*[45] observed a different result, demonstrating a reduced hospital stay in the BTS group.

Arezzo *et al*[46] found in their high-quality meta-analysis published in 2017 a significantly lower rate of temporary and definitive stomas (33.9% *vs* 51.4%, $P < 0.001$ and 22.2% *vs* 35.2%, $P = 0.003$), while no difference in the 60-d mortality was observed.

Only a few studies analyzed the cost-effectiveness between using SEMS for BTS and ES[10]. Allievi *et al*[47] and Neo *et al*[48] concluded that more data about cost-effectiveness are needed.

Update

The updated review of Hiyoshi *et al*[49] demonstrated that the use of SEMS was associated with low hospital mortality, a higher rate of primary anastomosis and decreased stoma rate. For these reasons after colonic stenting for BTS, patients often have a better quality of life compared with immediate resection[50]. Better short-term outcomes of the BTS group were confirmed by Spannenburg *et al*[51]. Higher primary anastomosis, lower 30-d mortality rate, lower overall complications rate and shorter hospital stay were reported.

In June 2022, a study that compared BTS to diverting stoma was published[52]. Seven studies were included, and 1358 patient were recruited (646 in the first group and 712 in the second group). A lower Clavien-Dindo I/II complication rate was highlighted in the BTS group (8.68% *vs* 16.85%, $P = 0.004$), while the III-IV grade were similar (7.69% *vs* 8.79%, $P = 0.37$). There were no differences in short-term mortality, 3-year OS and permanent stoma rate.

LONG-TERM OUTCOMES

Even though SEMS for BTS short-term outcomes have been quite established, the long-term outcomes still remain uncertain. In the last few years, the literature on using SEMS for BTS focused on oncological outcomes. The DFS is the time between surgery and discovery of new cancer signs, while the OS is the time between surgery to death. In the early 2000s, Kim *et al*[53] suspected that SEMS insertion could negatively impact oncological outcomes.

Some authors tried to explain the mechanism. Some authors hypothesized that SEMS manipulation could cause a microperforation that may lead to peritoneal carcinomatosis. Other authors hypothesized that tumor compression was the cause of hematogenous diffusion[54]. Maruthachalam *et al*[55] found an increased expression of cytokeratin 20 mRNA (marker of tumor cells) in patients after stent insertion.

Amelung *et al*[56] found no significant differences in recurrence rate and 3-year and 5-year OS. Rodrigues-Pinto *et al*[57] also found no differences in tumor recurrence, recurrence-free survival and OS between the ES and BTS groups. The same result was also obtained by Matsuda *et al*[6] and Gibor *et al* [58].

These results were strongly supported by Arezzo *et al*[46] and Amelung *et al*[56]. The first was a multicentric prospective randomized trial conducted by the European Association for Endoscopic Surgery. The second was a meta-analysis in which no differences between the two groups in terms of 3-year and 5-year DFS and in 3-year and 5-year OS were confirmed.

However, a few studies showed differences in long-term oncological outcomes. In 2019 Foo *et al*[54] presented a higher distant recurrence rate in the BTS group (25.3% *vs* 15.0%, P = 0.046) and overall recurrence rate in the BTS group (37.0% *vs* 25.9%, P = 0.049). A 5-year follow-up is usually described in all studies, whereas Verstockt *et al*[59] presented a 1-year, 2-year, 3-year, 5-year and 10-year OS for all patients regardless of stage.

In recent literature, the cost-effectiveness has also been considered[60]. The American Society for Gastrointestinal Endoscopy guidelines considered the use of stent for BTS more cost-effectiveness than ES[10]. However, little data about this topic are available[47].

Update

According to Cirocchi *et al*[7], the overall recurrence and 3-year OS rates are similar for both the ES and BTS groups. In another recent study, 3-year and 5-year DFS and OS were not different despite a higher number of lymph nodes harvested in the BTS group than the ES group[51].

In the ESCO trial[8], neither OS nor DFS differed in the BTS and ES groups in a 36-mo follow-up study. However, as it has been reported in this paper, one randomized trial showed an increased rate of malignant recurrence[61]. The contradictory data need a well conducted prospective, randomized trial. The inclusion criteria used by ESCO were colonic cancer between the splenic flexure and 15 cm from the anal margin and diagnosed by computed tomography. Similar long-term oncological outcomes were observed. A significant time to progression was observed in the descending colon, possibly because it was the easiest endoscopic procedure (compared to flexure and sigmoid). No differences in terms of time to progression, DFS and OS were observed considering age, sex, body mass index and American Society of Anesthesiologists score[8].

In February 2022, a multicentric study[62] including 564 patients was published. The results showed the "non-inferiority" of BTS *vs* ES in terms of OS (P = 0.012). However, in another a recent study[63] considering only stage II and III patients, a higher frequency of distant metastatic recurrence was shown in BTS group than in the surgery alone group (30.4% *vs* 13.3%, P = 0.035).

In 2022, Yamada *et al*[64] tried to explain how tumor manipulation may worsen the prognoses in CRC patients after SEMS insertion. Seven days after stent insertion the cfDNA, ctDNA and serum lactate dehydrogenase levels were significantly higher. This indicated that SEMS injures cancer and spreads damage-associated molecular patterns released by necrotic cells that induce sterile inflammation. SEMS placement seems to induce unfavorable gene circulation, which results in an microenvironment associated with cancer progression. According to this last study, angiogenesis is also induced by cancer manipulation *via* miR-9 downregulation.

According to some authors, using a standardized and reproducible SEMS insertion method is essential for reducing the perforation rate[31].

Veld *et al*[65] compared SEMS for BTS with decompressing stoma bridge to resection instead of ES. The authors concluded that the two techniques have similar intermediate-term oncological outcomes [65].

A comprehensive literature review compared SEMS for BTS long-term outcomes with decompressing stoma for BTS and ES. The authors found that colonic stent and decompressing stoma may lead to better 5-year OS and DFS than ES. The decompressing stoma may have a better 5-year OS than the BTS strategy. According to these data, Tan *et al*[66] recommended decompressing stoma as the best choice for left-sided colonic obstruction.

CONCLUSION

In 2022, the BTS strategy is considered a safe strategy, and many studies have demonstrated better short-term outcomes than ES. By using a stent for BTS, it is possible to obtain an increased rate of primary anastomosis *vs* stoma rate, a laparoscopic approach *vs* open approach and a shorter postoperative stay.

The endoscopic stent placement is not a simple procedure, and it requires specific skills[57]. The most recent ESGE guidelines recommend that colonic stenting should be performed by an operator with competence both in colonoscopy and fluoroscopic technique[22]. The stent insertion could be followed by early (< 30 d) or late complications (> 30 d), such as migration, perforation, bleeding and obstruction. However severe adverse events only occur in < 5% of procedures[10]. Stents could be covered or uncovered, with covered stents having a lower obstruction rate[27].

The use of a stent for BTS changes an ES into an elective surgery. The role of BTS has been analyzed for both short-term and long-term outcomes. The short-term outcomes are represented by higher laparoscopic approaches *vs* open surgery[42,43], higher rate of anastomosis *vs* stoma rate[41,46,67], 30-d post-surgery complications and hospital stay[44]. The long-term outcomes include the DFS, the progression-free survival and OS.

Almost all articles about SEMS for BTS from the late 1990s to 2010 focused on the short-term outcomes. After stent placement in an elective setting, surgery can be completed with a laparoscopic approach. In addition, a higher rate of primary anastomosis and lower rate of temporary or definitive stoma rates improve patient quality of life[46].

Currently, more focus is being place on long-term outcomes than short-term outcomes. Initially, gastroenterologists and surgeons were enthusiastic due to the excellent short-term results from the use of SEMS for BTS. However, conflicting data about the worsening of OS and DFS due to BTS curbed the initial enthusiasm[68]. Although there are many hypotheses, the exact biological mechanism has not been described. The use of a stent for BTS seems to be burdened by a higher rate of perforations and microperforations resulting in cancer spread[64]. Most articles only have 1-year to 3-year or 5-year follow-up. Some rare cases have longer periods[59].

Because of all these contrasting data, international guidelines do not agree about using a stent for BTS as the gold standard. The American guidelines suggest the use of a stent for BTS as the gold standard [10], while the European guidelines suggest the surgical resection and the use of SEMS for BTS as possible treatments in patients with left-sided obstructing colonic cancer[22].

Some of the most important topics for further studies are the national and international agreement on therapeutic algorithm of treatment for patients with left-sided obstructive colonic cancer and a more detailed cost-benefit analysis. Furthermore, considering literature after the 2020, it could be interesting to prepare a specific study to understand the impact of the COVID-19 pandemic impact on the use of SEMS for BTS.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Machine learning-assisted ensemble analysis for the prediction of urinary tract infection in elderly patients with ovarian cancer after cytoreductive surgery

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Abstract

BACKGROUND

Urinary tract infection (UTI) is a common type of postoperative infection following cytoreductive surgery for ovarian cancer, which severely impacts the prognosis and quality of life of patients.

AIM

To develop a machine learning assistant model for the prevention and control of nosocomial infection.

METHODS

A total of 674 elderly patients with ovarian cancer who were treated at the Department of Gynaecology at Jingzhou Central Hospital between January 31, 2016 and January 31, 2022 and met the inclusion criteria of the study were selected as the research subjects. A retrospective analysis of the postoperative UTI and related factors was performed by reviewing the medical records. Five machine learning-assisted models were developed using two-step estimation methods from the candidate predictive variables. The robustness and clinical applicability of each model were assessed using the receiver operating characteristic curve, decision curve analysis and clinical impact curve.

RESULTS

A total of 12 candidate variables were eventually included in the UTI prediction model. Models constructed using the random forest classifier, support vector machine, extreme gradient boosting, and artificial neural network and decision tree had areas under the receiver operating characteristic curve ranging from 0.776 to 0.925. The random forest classifier model, which incorporated factors such as age, body mass index, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia, had the highest predictive accuracy.

CONCLUSION

These findings demonstrate that the machine learning-based prediction model developed using the random forest classifier can be used to identify elderly patients with ovarian cancer who may have postoperative UTI. This can help with treatment decisions and enhance clinical outcomes.

Key Words: Cytoreductive surgery; Machine learning; Ovarian cancer; Risk factors; Urinary tract infection

Core Tip: Using a machine learning-based algorithm, we developed a feasible and robust method to identify factors that are significant for predicting urinary tract infections. The random forest classifier was especially robust and can improve the prediction and early detection of urinary tract infections in patients with ovarian cancer. In addition, the five most crucial factors were age, body mass index, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia. Clinicians may find it extremely helpful to assess the individualised risk of urinary tract infections in clinical practice by incorporating the presentation of simple clinical data.

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INTRODUCTION

Ovarian cancer is a gynaecological malignant tumour with the highest degree of malignancy and mortality[1]. Approximately 70%–80% of patients have advanced to the middle and late stage at the initial diagnosis owing to the asymptomatic nature of ovarian cancer in the early stage and lack of sensitive screening methods. In addition, 80% of patients with ovarian cancer experience a relapse within 1-2 years after surgery[2,3]. According to the statistics of the International Union of Obstetrics and Gynaecology, patients with ovarian cancer have a 5-year overall survival rate of < 40%, and a 5-year clinical stage IV survival rate of < 5%[4,5]. Currently, the first-line treatment for ovarian cancer is carboplatin combined with paclitaxel platinum chemotherapy following surgery, with a clinical remission rate of 60%–80%[6-8].

Advanced ovarian cancer is surgically treated with tumour cytoreductive surgery, which is the most effective surgical procedure[8]. Tumour cytoreductive surgery with a satisfactory tumour reduction ratio can prolong the survival time of patients and improve their overall survival rate. However, the scope of surgical resection includes not only ovaries, uterus and omentum but also pelvic and abdominal metastases and affected lymph nodes with a diameter of > 2 cm[9]. The operation is challenging, the injury obtained from the procedure is significant, and there are numerous complications since the procedure often involves the intestinal tract, the urinary tract and pelvic vessels. Additionally, some patients must undergo 2-3 courses of neoadjuvant chemotherapy prior to the surgery to have sufficient operation conditions[10]. The postoperative rehabilitation process and the quality of life of patients will suffer significantly from the high incidence of postoperative complications.

Urinary tract infection (UTI) is a common type of postoperative infection following tumour cell reduction surgery for ovarian cancer. It is related to the surgical procedure and the unique physiological structure of the female urinary tract[11,12]. Elderly patients with ovarian cancer have a higher incidence of postoperative UTI owing to their weak immune system, poor organ reserve capacity and a high proportion of basic diseases[13]. The evaluation of related factors is crucial for the prevention and management of nosocomial infection. However, there is no specific study on the related factors of UTI in elderly patients with ovarian cancer who underwent cytoreductive surgery at home and abroad.

Nowadays, predictive models based on advanced algorithms have been gradually applied to the medical field, which also enables many diseases to be detected and diagnosed early[14,15]. Among them, the machine learning (ML) algorithm relies on repeated iterative operations to accurately output the results, so it can improve the accuracy and robustness of prediction. Given the superior ability of the

ML-based algorithm to improve the accuracy of muscular invasion prediction, we applied the ML-assisted decision-support model to assess the risk of UTI using clinical parameters and direct clinical decision-making prior to treatment decisions.

MATERIALS AND METHODS

Patient selection

As the research subjects, 674 elderly patients with ovarian cancer who received treatment at the Department of Gynaecology at Jingzhou Central Hospital between January 31, 2016 and January 31, 2022 and met the inclusion criteria were selected. A retrospective analysis of the postoperative UTI and related factors was performed using medical records. The inclusion criteria for patients were as follows: (1) All patients met the diagnostic criteria in the clinical practice guidelines for ovarian cancer developed by the National Comprehensive Cancer Network and were diagnosed by imaging examination and postoperative pathology[16]; (2) All the patients were older than 60-years-old. The clinical stages were stage III and above, and the pelvic and abdominal masses were fixed; and (3) All the patients were scheduled for cytoreductive surgery. The clinical data were complete, and the postoperative hospital stay exceeded 5 d. The exclusion criteria for patients were as follows: (1) Patients undergoing secondary cytoreductive surgery for recurrent ovarian cancer; (2) Patients with liver and kidney insufficiency, cardiovascular and cerebrovascular accidents, blood diseases, autoimmune diseases or immunodeficiency diseases and other malignant tumours; (3) Patients diagnosed with acute and chronic infection prior to surgery; and (4) Patients who had long-term usage of immunosuppressants or glucocorticoids. The guidelines of the Helsinki Declaration (2013 revision) were followed by the study protocol. It was approved by the Institutional Review Committee of Jingzhou Central Hospital (JZ-2022014). Owing to its traceability, patient information was managed with the utmost confidentiality, and informed consent was waived. The workflow for patient selection and model construction is summarized in Figure 1.

Diagnosis of postoperative urinary tract infection

The diagnostic criteria were as follows: The patient had urinary tract irritation symptoms such as frequent micturition, urgency and pain following the surgery. By microscopic examination of the urine sediment, the average number of leukocytes per high-power visual field was ≥ 5, and the urine pathogen was present. Based on a diagnosis of UTI, patients were divided into an infection group and a non-infection group.

Data collection and quality assessment

The following data were collected from all patients: age, body mass index (BMI), catheter retention time, catheter intubation times, operation time, intraoperative blood loss, length of hospital stay, diabetes, hypertension, prophylactic use of antibiotics and postoperative hypoproteinaemia. In most cases, the median was applied to variables with missing values. A variable was excluded from variable screening for the final model if ≥ 10% of its values were missing.

Development and validation of ML-based models

The data were randomly divided into a training set (70%) and a verification set (30%) to verify the prediction model. The inclusion principle of variables reported in previous studies was followed to screen variables. The principle of ‘OOB error’ was employed to screen the model variables (*i.e.* characteristic variables)[17], as follows: Gini (D) = $1-\sum_{(i=1)}^{m} P_i^2$. If the Gini index was small, the probability of selecting mixed samples in the set was low, that is, the higher the purity of the set was and vice versa. However, the Gini index approaches zero if every sample in the set was of the same class. Based on the above algorithm principles, we have included five commonly used machine algorithm prediction models in this study, namely random forest classifier (RFC), support vector machine, extreme gradient boosting, artificial neural network (ANN) and decision tree (DT). Among them, RFC and DT are based on the algorithm principle of “branching and pruning,” while ANN is based on “hidden layer” iteration. Support vector machine and extreme gradient boosting are also based on their iterative algorithm principle.

Prediction efficiency evaluation of ML-based models

The optimal subset variables for the modelling were obtained based on the intersection of variable sets. The receiver operating characteristic curve was used to evaluate the prediction accuracy of the model in the training and validation set. The discrimination ability of each model was quantified by the area under the receiver operating characteristic curve, decision curve analysis and clinical impact curve.

Statistical analysis

For descriptive analysis, median (interquartile range) and frequencies (%) were assessed for continuous

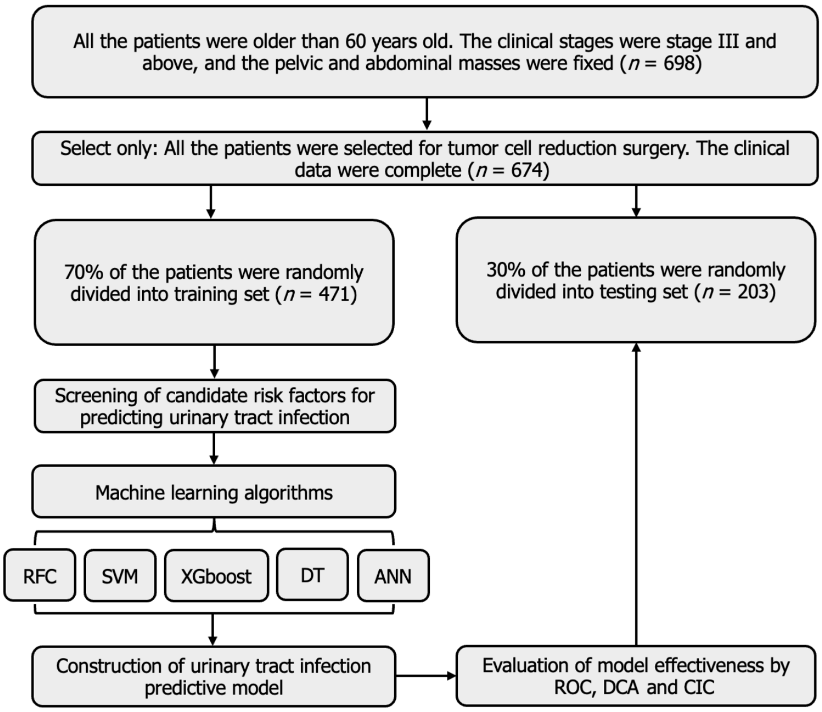

Figure 1 Flow chart of the patient selection and data process. ANN: Artificial neural network; CIC: Clinical impact curve; DCA: Decision curve analysis; DT: Decision tree; RFC: Random forest classifier; ROC: Receiver operating characteristic curve; SVM: Support vector machine; XGboost: Extreme gradient boosting.

and categorical variables, respectively. Bonferroni corrected probability values were used to compare the qualitative data[18]. Wilcoxon rank-sum test or χ^2 test was used to compare the differences between diverse groups. The best subset of randomly selected explanatory variables or features was used to further divide each node during the selecting process, and the class prediction values generated by each tree were collected. Finally, the candidate variables of the prediction model, namely the Gini index, were determined according to the weight. All analysis was performed using the Python programming language (version 3.9.2, Python Software Foundation, https://www.python.org/) and R project for statistical computing (version 4.0.4, http://www.r-project.org/). All P values were two-tailed, and P < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

The comprehensive clinical features and baseline data of 674 elderly patients with ovarian cancer are presented in Table 1. Using the caret package, patients were randomly divided into a training set (70%, n = 471) and a validation set (30%, n = 203) for internal validation of the model. As presented in Table 1 and Supplementary Table 1, 96 patients had postoperative UTI, with an infection rate of 14.24%. The clinical symptoms and signs of the patients were primarily urinary tract irritation, fever, poor urination or urinary retention, renal percussion pain and urethral mouth itching. In addition, there were significant differences in catheter retention time, catheter intubation times, intraoperative bleeding, length of hospital stay, the proportion of patients with diabetes and the incidence of postoperative hypoproteinaemia (P < 0.05) between the infection group and the non-infection group.

Selection of candidate variables

Feature selection is the aspect of ML that concentrates on selecting candidate variables[19]. The iterative analysis screened the candidate covariates of each algorithm. We executed 13 variables *via* Pearson correlation analysis. The correlation matrix revealed that UTIs significantly correlated with image factors and some clinical variables (Figure 2A). In addition, every significant candidate variable, such as age, BMI, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia, contributed to the ML-based model (Figure 2B). These seven were the top predictors, which were consistent with the findings of the correlation analysis.

Table 1 Baseline demographic and clinicopathological characteristics of patients, *n* (%)

Variables	Training set				Testing set			
	Overall, *n* = 471	Yes, *n* = 70	No, *n* = 401	*P* value	Overall, *n* = 203	Yes, *n* = 26	No, *n* = 177	*P* value
Age [median (IQR)], yr	64.00 (63.00, 66.00)	69.00 (67.00, 71.00)	64.00 (62.00, 65.00)	< 0.001	64.00 (62.00, 65.50)	68.50 (65.25, 70.75)	63.00 (62.00, 65.00)	< 0.001
BMI [median (IQR)], kg/m^2	23.00 (22.00, 24.00)	24.00 (23.00, 25.00)	23.00 (22.00, 24.00)	< 0.001	23.00 (22.00, 24.00)	25.00 (23.00, 26.00)	23.00 (22.00, 24.00)	< 0.001
Catheter [median (IQR)], d	8.00 (7.00, 10.00)	13.00 (10.00, 14.00)	8.00 (7.00, 9.00)	< 0.001	8.00 (7.00, 9.00)	13.00 (11.00, 13.00)	8.00 (6.00, 9.00)	< 0.001
Catheter intubation times								
≥ 3	148 (31.4)	49 (70.0)	99 (24.7)	< 0.001	59 (29.1)	23 (88.5)	36 (20.3)	< 0.001
< 3	323 (68.6)	21 (30.0)	302 (75.3)		144 (70.9)	3 (11.5)	141 (79.7)	
Operation time [median (IQR)], h	3.60 (2.90, 4.40)	3.80 (3.10, 4.50)	3.60 (2.80, 4.30)	0.061	3.70 (2.90, 4.60)	3.85 (2.93, 4.60)	3.70 (2.90, 4.50)	0.373
Blood loss [median (IQR)], mL	476.00 (434.50, 515.50)	627.00 (592.75, 658.75)	465.00 (429.00, 499.00)	< 0.001	470.00 (432.00, 504.00)	646.00 (616.25, 670.00)	461.00 (426.00, 494.00)	< 0.001
Hospitalization [median (IQR)], d	11.00 (9.00, 13.00)	15.00 (14.00, 17.00)	10.00 (8.00, 12.00)	< 0.001	10.00 (8.00, 12.00)	16.00 (15.00, 17.00)	10.00 (8.00, 12.00)	< 0.001
Diabetes								
Yes	162 (34.4)	57 (81.4)	105 (26.2)	< 0.001	59 (29.1)	22 (84.6)	37 (20.9)	< 0.001
No	309 (65.6)	13 (18.6)	296 (73.8)		144 (70.9)	4 (15.4)	140 (79.1)	
Hypertension								
Yes	283 (60.1)	45 (64.3)	238 (59.4)	0.519	132 (65.0)	19 (73.1)	113 (63.8)	0.483
No	188 (39.9)	25 (35.7)	163 (40.6)		71 (35.0)	7 (26.9)	64 (36.2)	
Antibiotics								
Yes	295 (62.6)	47 (67.1)	248 (61.8)	0.477	128 (63.1)	16 (61.5)	112 (63.3)	1
No	176 (37.4)	23 (32.9)	153 (38.2)		75 (36.9)	10 (38.5)	65 (36.7)	
Hypoproteinaemia								
Yes	122 (25.9)	53 (75.7)	69 (17.2)	< 0.001	54 (26.6)	22 (84.6)	32 (18.1)	< 0.001
No	349 (74.1)	17 (24.3)	332 (82.8)		149 (73.4)	4 (15.4)	145 (81.9)	
NACT								
Yes	293 (62.2)	18 (25.7)	275 (68.6)	< 0.001	133 (65.5)	12 (46.2)	121 (68.4)	0.045
No	178 (37.8)	52 (74.3)	126 (31.4)		70 (34.5)	14 (53.8)	56 (31.6)	

BMI: Body mass index; IQR: Interquartile range; NACT: Neoadjuvant chemotherapy.

Construction of ML-based UTI predictive model

Positive or negative training results for each patient were entered for training data, and the final judgment result was the output, as indicated in the following formula: Gini(D)= 1-∑_(i = 1)^m P_i^2. The RFC algorithm represents a computational method for effectively navigating the free parameter space to obtain a robust model (Figure 3A). The variable Gini index in the RFC model is presented in Supplementary Table 2. The top seven candidate variables were age, BMI, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia, which were consistent with the predicted results. In addition, data mining through the DT model, as demonstrated by impurity analysis: Gini (p) = ∑_(K = 1)^K [Pk(1-Pk)], was advantageous. At the branch of DT, age and catheter functioned as the irreplaceable weight in addition to clinical factor indicators (Figure 3B). In contrast, the RFC model outperformed the ANN model, which outperformed other models, in terms of prediction efficiency (Figure 4 and Supplementary Table 3).

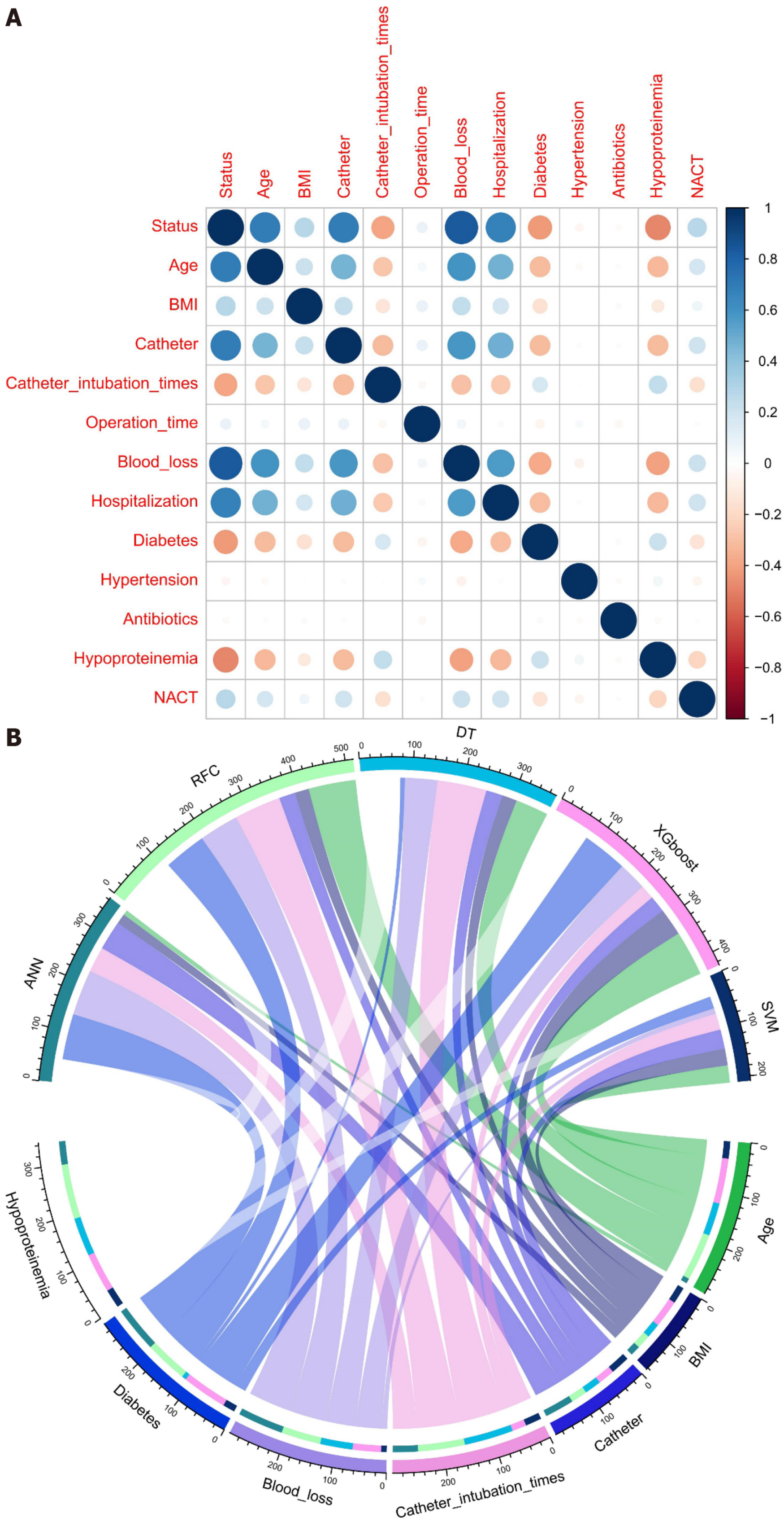

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Figure 2 Variable screening and weight allocation. A: Variable screening; B: weight allocation. ANN: Artificial neural network; BMI: Body mass index; DT: Decision tree; NACT: Neoadjuvant chemotherapy; RFC: Random forest classifier; SVM: Support vector machine; XGboost: Extreme gradient boosting.

Comparison across ML-based models

We used five supervised learning models for UTI assessment to investigate whether ML-based models

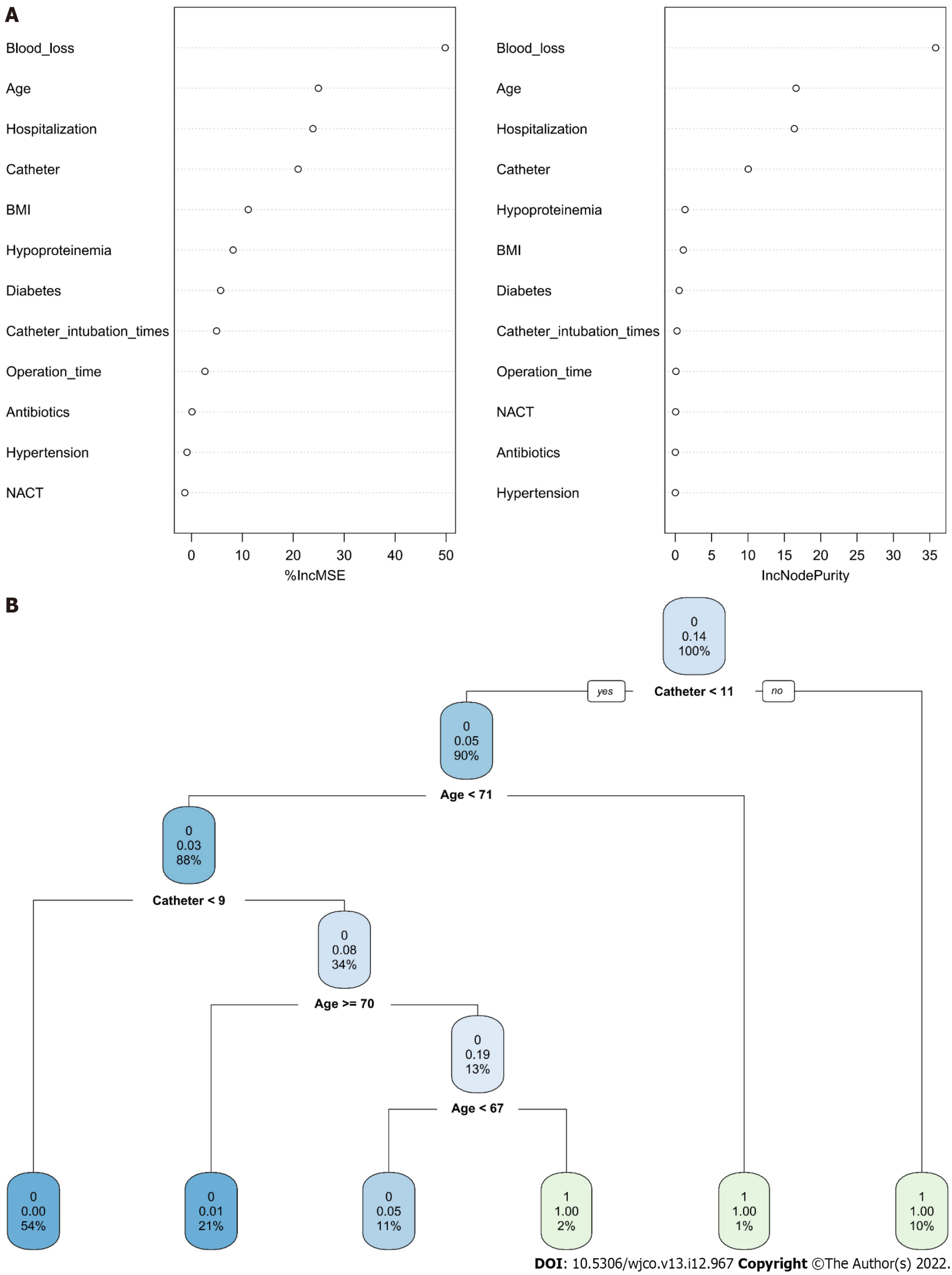

Figure 3 Predictive model visualization based on machine learning-based algorithm. A: The random forest classifier algorithm represents a computational method for effectively navigating the free parameter space to obtain a robust model; B: At the branch of decision tree, age and catheter functioned as the irreplaceable weight in addition to clinical factor indicators. BMI: Body mass index; NACT: Neoadjuvant chemotherapy.

can improve prediction performance. The RFC model demonstrated a strong prediction performance in the training and validation cohorts based on decision curve analysis (Figure 5). In addition, the area under the curve of the RFC models peaked when the seven variables were added, followed by those of

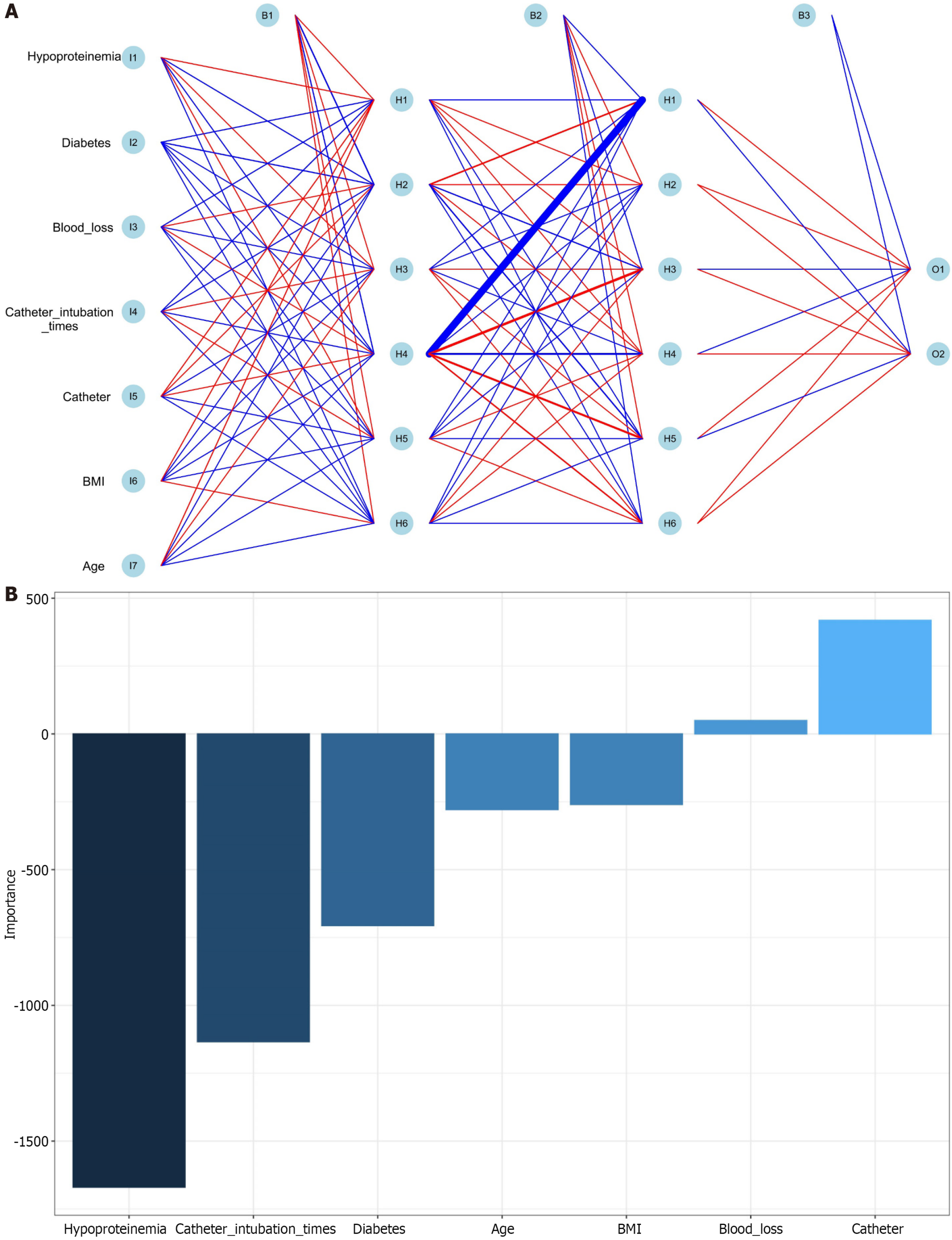

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Figure 4 Predictive model visualization based on artificial neural network algorithm. BMI: Body mass index.

ANN, DT, support vector machine and extreme gradient boosting (Table 2 and Supplementary Table 4). Undoubtedly, RFC outperformed the generalised linear model in terms of prediction accuracy. Thus, both RFC and DT (ML-assisted decision-support) models were used to guide UTI prediction using the iterative algorithm analysis of supervised learning.

Table 2 Receiver operating characteristic curve analyses for predicting urinary tract infection in each machine learning-based model

Model	Training set			Testing set		
	AUC mean	AUC 95%CI	Variables[1]	AUC mean	AUC 95%CI	Variables[1]
RFC	0.925	0.868-0.982	7	0.918	0.861-0.975	7
SVM	0.787	0.730-0.844	7	0.779	0.722-0.836	7
DT	0.776	0.719-0.833	7	0.769	0.712-0.826	7
ANN	0.879	0.822-0.936	6	0.854	0.797-0.911	6
XGboost	0.797	0.740-0.854	7	0.788	0.731-0.845	7

[1]Variables included in the model. ANN: Artificial neutral network; AUC: Area under the curve; CI: Confidence interval; DT: Decision tree; RFC: Random forest classifier; SVM: Support vector machine; XGboost: Extreme gradient boosting.

Internal validation of the optimal predictive model

We also used the clinical impact curve to assess the accuracy to further validate the RFC model's ability to predict outcomes. The clinical impact curve revealed that UTI stratification was achieved in the training cohorts (Supplementary Figure 1). These were consistent with the results of validation cohorts, indicating that RFC performed best in terms of discrimination, calibration and overall performance, in particular the candidate systemic inflammation markers that were highly relevant to UTIs.

DISCUSSION

This study's findings indicated that the factors influencing the risk of UTI in elderly patients with ovarian cancer after tumour cell reduction include not only the patients' basic diseases but also their indwelling catheter and postoperative nutritional level. There has been a lack of specialised research on UTIs after tumour cell reduction in recent years, and some researchers have examined the operation or resection of patients with ovarian cancer. These findings demonstrated that the most common clinical manifestations of patients with UTI are urinary tract irritation, urinary retention, urethral mouth itching and urine turbidity, which is consistent with the results of a previous study[20]. However, the incidence of UTIs reported in these studies ranges from < 10% to > 40%. The infection rate reported in this study was 14.24%, which is considered moderate; this may be due to the exclusion of patients with severe basic diseases such as liver and kidney dysfunction[21,22]. In addition, concerning infection-related factors, these reports have drawn similar conclusions as this study, albeit they also stated that age, intubation times, length of hospital stay, paraaortic lymph node dissection and intestinal resection, haemoglobin and other factors can all affect the risk of infection.

In general, cytoreductive surgery is a relatively traumatic procedure for advanced ovarian cancer, and the scope of the operation is likely to involve the urinary system, causing a significant increase in the risk of postoperative UTI. Simultaneously, the risk factors for postoperative UTI in elderly patients differ from those in young and middle-aged patients. Therefore, the research objects with high heterogeneity are selected for analysis, and the demonstrability and repeatability of the results are insufficient. Furthermore, a thematic analysis for the patient population with specific surgical procedures and similar conditions and susceptibility factors should be performed. Considering this situation, this study included elderly patients with ovarian cancer who had undergone cytoreductive surgery as the research. Our findings indicated that actively controlling catheter-related UTIs and correcting postoperative malnutrition were important links to preventing and controlling UTIs in the elderly after ovarian cancer cell reduction.

Through clinical observation, researchers have discovered that postoperative UTI caused by an indwelling catheter is one of the most common postoperative infections in clinics in recent years. The operation, catheter selection, bladder flushing and patient factors are the main causes of infection, and catheter placement time, difficulty in catheter intubation, multiple intubations, previous catheter retention history, long anaesthesia time, history of diabetes, age, consciousness disorder improper bladder flushing, gastrointestinal decompression, enema, long replacement time of urine collection bag and other factors are related to postoperative catheter-related UTI[23]. Numerous studies have demonstrated that the time of catheter placement is an independent risk factor for postoperative UTI. Thus, to effectively prevent catheter-related UTI, it is necessary to strictly control the indications of a long-term indwelling catheter, reduce urethral injury, improve the skills of operators, prevent retrograde infection, improve the tightness of the catheter system and ensure the patency of the catheter system in clinical work.

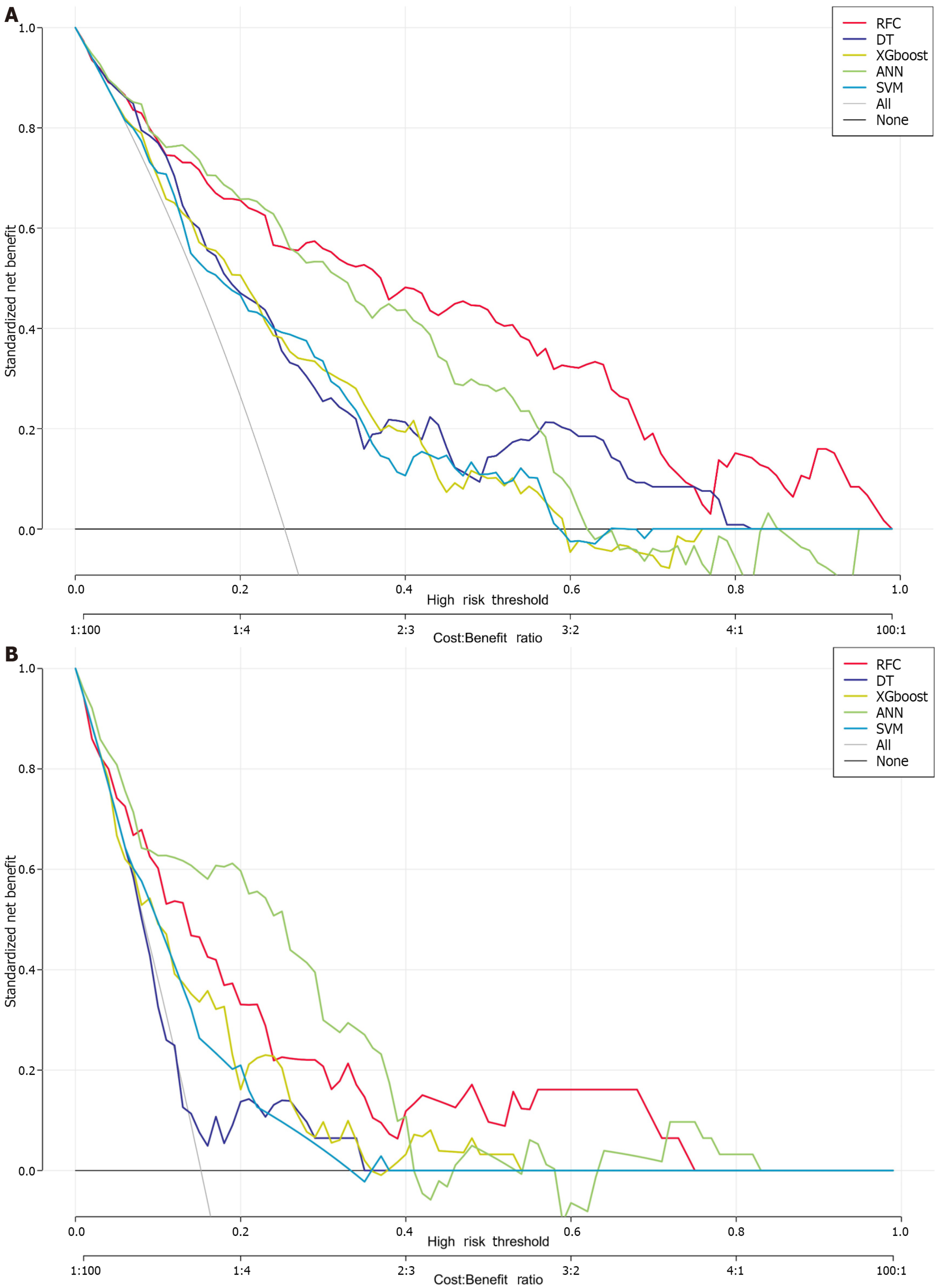

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Figure 5 Prediction performance of candidate models based on machine learning-based algorithm. ANN: Artificial neural network; DT: Decision tree; RFC: Random forest classifier; SVM: Support vector machine; XGboost: Extreme gradient boosting.

One of the most common complications after major surgery is hypoproteinaemia. Its causes are complex, and it is closely linked to surgical trauma. Operation post-stress is related to infection and other factors[24,25]. Simultaneously, plasma albumin level in severe patients is correlated with the expression of serum inflammatory factors and peripheral blood T cell subsets. Hypoproteinaemia can improve the degree of inflammatory stress, cause immune dysfunction, significantly increase the risk of bacterial and fungal infection and have a serious adverse impact on the disease outcome[26,27]. In patients undergoing surgery for a malignant tumour or organ function decompensation, postoperative hypoproteinaemia can increase the incidence and mortality of complications, such as postoperative infection, and seriously impact the surgical efficacy. The incidence of postoperative complications significantly decreases as plasma albumin levels rise. Therefore, early postoperative nutritional support is an important link in the treatment and prevention of infection in elderly patients with ovarian cancer. Early intravenous nutrition support should be strengthened for patients who cannot use early enteral nutrition to correct the negative nitrogen balance caused by surgical stress and maintain normal nutrition levels in particular.

It is noteworthy that, owing to the limitations of clinical medical records, the risk factors associated with cytoreductive surgery for ovarian cancer in the elderly examined in this study are not comprehensive, which is a flaw in this study. In addition to the relevant factors analysed in this study, ascites volume, operation scope and other factors will also affect it. Laparoscopic cytoreductive surgery for advanced ovarian cancer is becoming more prevalent as laparoscopic technology advances, which reduces the risk of surgical trauma and postoperative infection to some extent. These factors must be researched and analysed further.

CONCLUSION

In conclusion, using an ML-based algorithm, we created a feasible and robust method for identifying factors important for predicting UTIs. The RFC in particular, which can improve the prediction and early detection of UTIs in patients with ovarian cancer, was robust. In addition, age, BMI, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia were five crucial factors. In clinical practice, incorporating the presentation of simple clinical data may be helpful for clinicians to identify the individualised risk of UTI.

ARTICLE HIGHLIGHTS

Research background

Nowadays, predictive models based on advanced algorithms have been gradually applied to the medical field, which also enables many diseases to be detected and diagnosed early. Among them, the machine learning (ML) algorithm relies on repeated iterative operations to accurately output the results. Therefore, it can improve the accuracy and robustness of prediction.

Research motivation

Given the superior ability of the ML-based algorithm to improve the accuracy of muscular invasion prediction, we applied the ML-assisted decision-support model to assess the risk of urinary tract infection (UTI) using clinical parameters and direct clinical decision-making prior to treatment decisions.

Research objectives

We developed an ML assistant model for the prevention and control of nosocomial infection.

Research methods

A total of 674 elderly patients with ovarian cancer treated between January 31, 2016 and January 31, 2022 and met the inclusion criteria of the study were selected as the research subjects. A retrospective analysis of the postoperative UTI and related factors was performed by reviewing the medical records. Five ML-assisted models were developed using two-step estimation methods from the candidate predictive variables. The robustness and clinical applicability of each model were assessed using the receiver operating characteristic curve, decision curve analysis and clinical impact curve.

Research results

A total of 12 candidate variables were eventually included in the UTI prediction model. Models constructed using the random forest classifier (RFC), support vector machine, extreme gradient boosting, artificial neural network and decision tree had areas under the receiver operating characteristic curve ranging from 0.776 to 0.925. The RFC model, which incorporated factors such as age, body mass index, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia, had the highest predictive accuracy.

Research conclusions

These findings demonstrated that the ML-based prediction model developed using the RFC can be used to identify elderly patients with ovarian cancer who may have postoperative UTI. This can help with treatment decisions and enhance clinical outcomes.

Research perspectives

Using an ML-based algorithm, we developed a feasible and robust method to identify factors that are significant for predicting UTIs. The RFC, which can improve the prediction and early detection of UTIs in patients with ovarian cancer, was particularly robust. In addition, the five most crucial factors were age, body mass index, catheter, catheter intubation times, blood loss, diabetes and hypoproteinaemia. Clinicians may find it extremely helpful to assess the individualised risk of UTI in clinical practice by incorporating the presentation of simple clinical data.

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FOOTNOTES

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LETTER TO THE EDITOR

Circulating tumour DNA in gastrointestinal cancer in clinical practice: Just a dream or maybe not?

Andrea Pretta, Eleonora Lai, Clelia Donisi, Dario Spanu, Pina Ziranu, Valeria Pusceddu, Marco Puzzoni, Elena Massa, Mario Scartozzi

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Abstract

The evaluation of circulating tumor DNA (ctDNA) is increasingly integrated into the management of diagnosis and treatment of gastrointestinal cancer as it represents an innovative and minimally invasive biomarker that could allow us to reach clinical needs not met yet in randomized clinical trials. Recent research provided an interesting overview of the role of circulating tumor DNA in gastric, biliary, liver, pancreatic, and colorectal cancer. Data regarding upper gastrointestinal tumors are currently not practice changing. Tumor detection rates are low in the early stages, while in advanced stages ctDNA is useful for molecular tracking evaluation. Most of the evidence comes from colorectal cancer studies, where ctDNA was evaluated both in the early and advanced stages with the post-surgery minimal residual disease assessment and the response assessment, respectively. ctDNA qualifies as a promising tool in the era of precision medicine, with potential applications in the entire management of gastrointestinal cancer patients. Further evidence is needed to establish which setting may be influenced greatly by liquid biopsy in clinical practice.

Key Words: Circulating tumor DNA; Gastrointestinal cancer; Liquid biopsy; Esophageal cancer; Gastric cancer; Liver cancer; Bile duct cancer; Pancreatic cancer; Colorectal cancer

Core Tip: Circulating tumor DNA is a promising tool in the era of precision medicine, with several potential applications in the entire management of gastrointestinal malignancies. Further evidence is needed to assess in which setting liquid biopsy might have a greater impact in clinical practice.

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TO THE EDITOR

We read with great interest the minireview by Kirchweger *et al*[1], entitled "Circulating tumor DNA (ctDNA) for diagnosis, prognosis and treatment of gastrointestinal malignancies". This paper provides a comprehensive overview on available literature data regarding the potential role of ctDNA in the management of gastric, biliary tract, liver, pancreatic and colorectal cancer (CRC). The authors discuss the application of ctDNA detection from diagnosis to prognosis and treatment monitoring of each disease analysed, by critically presenting to the readers the advantages and limitations of this tool.

We strongly agree with authors that ctDNA represents an innovative, minimally invasive biomarker that might allow us to reach unmet clinical needs in clinical practice for gastrointestinal cancer patients if further validated in randomised clinical trials. Indeed, considering the dynamic nature of tumor biology and the genetic heterogeneity of diseases such as CRC, the serial assessments of biomarkers of interest through liquid biopsy might reflect the continuous changes of tumour itself and be useful to clinicians[2].

Notably, not a large amount of data is available about the application of ctDNA for diagnosis, as well as about its role in gastric and liver cancer. We greatly appreciate the authors' effort to analyse these particular aspects and cancer types which are not the main field of research for this topic.

Indeed, main evidences regard prognosis and treatment monitoring, both in early stages (detection of minimal residual disease) and in advanced stages. Moreover, the majority of evidences derive from CRC studies.

Recently, Bregni *et al*[3] showed that baseline ctDNA was an independent prognostic factor for disease free survival (HR 3.35, 95%CI: 1.15-9.77, P = 0.03) in stage III CRC patients treated with neoadjuvant conventional 5-fluorouracil, oxaliplatin and folinic acid (FOLFOX) followed by surgery +/- adjuvant FOLFOX in the PePiTA trial[4]. These findings derive from a small sample size (80 patients) but represent a starting point needing to be confirmed in larger trials focusing on early-stage CRC.

Surely, as highlighted by the authors, ctDNA has been extensively studied for tailoring treatment with anti-EGFR in further lines for RAS wild type metastatic CRC[5]. Our group recently explored the liquid biopsy-driven cetuximab rechallenge in a *RAS* and *BRAF* wild type selected population[6]. This strategy was confirmed to be effective and despite the small sample size, clinical outcome was consistent with the findings of phase II studies. Moreover, we observed that in addition to the molecular selection through ctDNA analysis for *RAS-BRAF*, long anti-*EGFR* free interval was a prospective selection criterion for this therapeutic option. Thus, the combination of ctDNA analysis plus clinical elements might be a winning strategy overcoming the limitations of a single tool.

As for pancreatic cancer, the identification of prognostic and predictive biomarkers is an urgent medical need. Unfortunately, despite extensive research no robust validated factors to guide treatment choice are available, except for *BRCA* status, and no effective agents have drastically improved the management of this disease, including immunotherapy[7-10]. For this reason, we strongly agree with the authors that ctDNA detection appears as an appealing instrument to guide therapeutic choices across different treatment lines, in order to improve clinical outcomes pancreatic cancer patients. Indeed, liquid biopsy has shown to be more sensitive than carbohydrate antigen199 levels in predicting prognosis and treatment response[11].

Moreover, ctDNA evaluation has been shown to be more sensitive than current gold standard radiological methods (computed tomography) in the evaluation of the tumor burden at staging (for any micro dissemination or lymph node involvement) and for relapses detection[12-13].

At the present time, data regard small groups of patients and require validation in larger trials.

In conclusion, ctDNA qualifies as a promising main actor in the precision medicine era, with potential applications in the whole management of gastrointestinal cancer patients. Further larger and prospective studies are needed to assess the real impact of liquid biopsy in clinical practice, but for now, potential benefits are likely to overcome its limitations.

FOOTNOTES

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