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ABOUT COVER

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MINIREVIEWS

Targeting *KRAS* in pancreatic adenocarcinoma: Progress in demystifying the holy grail

Ahmed Elhariri, Ahmed Alhaj, Daniel Ahn, Mohamad Bassam Sonbol, Tanios Bekaii-Saab, Christina Wu, Michael Scott Rutenberg, John Stauffer, Jason Starr, Umair Majeed, Jeremy Jones, Mitesh Borad, Hani Babiker

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Abstract

Pancreatic cancer (PC) remains one of the most challenging diseases, with a very poor 5-year overall survival of around 11.5%. Kirsten rat sarcoma virus *(KRAS)* mutation is seen in 90%-95% of PC patients and plays an important role in cancer cell proliferation, differentiation, metabolism, and survival, making it an essential mutation for targeted therapy. Despite extensive efforts in studying this oncogene, there has been little success in finding a drug to target this pathway, labelling it for decades as "undruggable". In this article we summarize some of the efforts made to target the KRAS pathway in PC, discuss the challenges, and shed light on promising clinical trials.

Key Words: Kirsten rat sarcoma virus; Targeted therapy; Pancreatic cancer; Drug resistance; Next generation sequencing; Clustered regularly interspaced short palindromic repeats

Core Tip: Kirsten rat sarcoma virus (*KRAS*) mutation is the hallmark of pancreatic cancer (PC) and an important therapeutic target. Approaches to target this oncogene has been challenging. We herein discuss the role of *KRAS* in development of PC, efforts made to target this pathway, and ongoing clinical trials.

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INTRODUCTION

In 2022, there was an estimated 62210 new pancreatic cancer (PC) cases and 49830 estimated deaths. PC is the fourth leading cause of cancer death in the United States[1]. PC is driven primarily by mutations in the Kirsten rat sarcoma virus (*KRAS*) gene, cyclin-dependent kinase inhibitor 2A, tumor protein 53, and mothers against decapentaplegic protein homolog 4. *KRAS* is one of the most frequently mutated oncogenes in human cancers. It is seen in more than 90% of PCs and more than 40% of colorectal and lung cancers[2]. 93% of all *KRAS* mutations occur at codon 12 (G12) with other common mutation sites at G13 and Q61. Missense mutation in glycine residues of G12 result in amino acid substitution, glycine substituted with aspartic acid (G12D), with valine (G12V), or with cysteine (G12C)[3]. The predominant mutation in PC is G12D followed by G12V (Figure 1)[4], but in lung cancer G12C is the most common. *KRAS* plays a major role in the development of PC and, as a result, there have been significant efforts to target the mutated *KRAS* pathway.

BACKGROUND

KRAS is a member of the rat sarcoma viral oncogene family (RAS), in addition to Neuroblastoma rat sarcoma virus and Harvey rat sarcoma virus. Identified in 1982, the *KRAS* is located on the short arm of chromosome 12[5,6]. It encodes two protein isoforms, KRAS-4B and KRAS-4A. Those are found in the inner side of the plasma membrane[7], and act as guanosine triphosphate (GTP)-binding proteins (G proteins), they bind guanine nucleotides that belong to the family of GTP-bound regulatory protein phosphatases (GTPase). An upstream signal *e.g.*, epidermal growth factor receptor (EGFR) stimulates the dissociation of guanosine diphosphate (GDP) from the GDP-bound G protein form, and allows the binding of GTP[8]. RAS functions as a binary switch, determined by two regulatory proteins called guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAP)[9]. KRAS binds to GDP in resting state due to its intrinsic GTPase activity. But with relevant stimuli, GEFs turn on signaling by catalyzing the exchange from a KRAS G-protein-bound GDP to GTP[10] (Figure 2). KRAS proteins can be activated by tyrosine kinase receptors, growth factors, chemokines, or calcium. This in turn activates multiple signaling pathways including the rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase (MAPK)-extracellular regulated protein kinases (ERK) (MAPK/ERK; MEK) signaling pathway, the phosphoinositide 3-kinase (PI3K)-protein kinase (AKT)-mammalian target of rapamycin (mTOR) signaling pathway, and others. These pathways result in cell proliferation and DNA synthesis (Figure 3).

Precursor lesions of pancreatic ductal adenocarcinoma (PDAC) include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm[11,12]. *KRAS* mutation was detected in 36% of PanIN-1A lesions and 87% of PanIN-2-3 lesions[13]. It was also found in 61% of patients with IPMN[14]. To study the role of *KRAS* in PC progression, scientists developed transgenic mice with inducible $KRAS^{G12D}$. Induction of oncogenic $KRAS^{G12D}$ altered normal epithelium and led to the development of precancerous lesions; on the other hand, inactivation of $KRAS^{G12D}$ in precursor lesions and during cancer progression led to disease regression[15]. These studies confirm the early role of *KRAS* mutation in the initiation and progression of precursor lesions into invasive PDAC as well as the correlation between frequency of *KRAS* mutation and degree of dysplasia.

KRAS mutation drives PC progression by resistance to apoptosis, induction of autophagy[16], immune evasion by downregulating major histocompatibility complex class I on tumor cells[17], and stimulating angiogenesis, resulting in cell survival and tumor progression.

TARGETED THERAPY

Upstream regulators

Some of the key regulators of KRAS include Son of Sevenless (SOS) and Src homology phosphatase 2 (SHP2). SOS is a GEF that activates KRAS, and SHP2 is a protein tyrosine phosphatase encoded by *PTPN11* that also promotes RAS activation, inhibiting either can delay tumor progression[18,19].

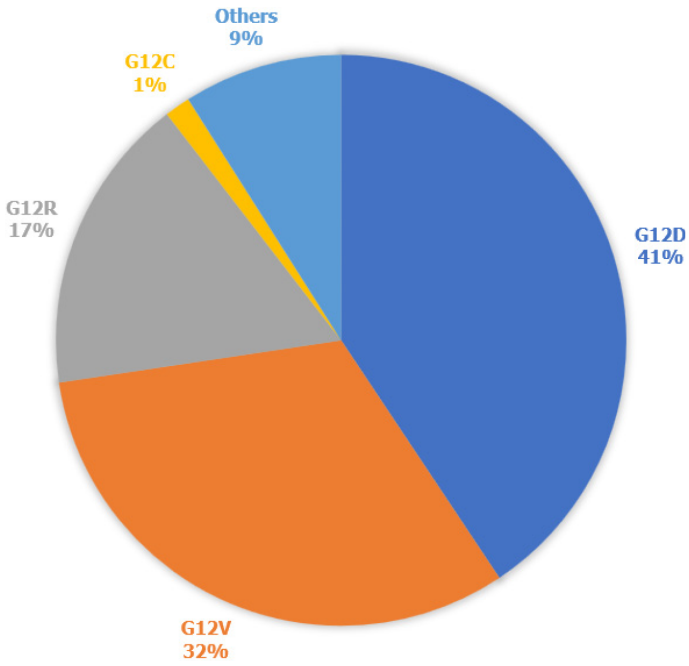

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Figure 1 Kirsten rat sarcoma virus mutations in pancreatic cancer. Types of Kirsten rat sarcoma virus (*KRAS*) mutations seen in pancreatic cancer, according to data publicly available on cBioPortal. 812 samples with altered *KRAS* collected from 5 pancreatic cancer studies. Others are A11T, A146T, A18V, G12A, G12I, G12L, G12S, G13C, G13D, G13H, G13P, G13R, L23V, Q61H, Q61K, Q61R.

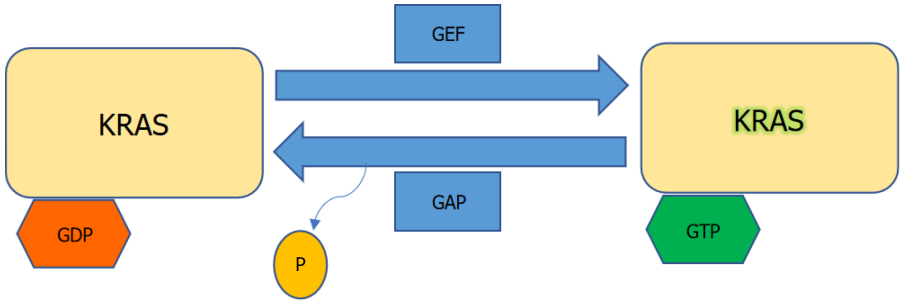

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Figure 2 Kirsten rat sarcoma virus activation. Kirsten rat sarcoma virus is activated when guanine nucleotide exchange factor displaces guanosine diphosphate from nucleotide binding site allowing guanosine triphosphate (GTP) binding and inactivated upon GTP hydrolysis by intrinsic GTP-bound regulatory protein phosphatases (GTPase) activity enhanced by GTPase activating protein. GTP: Guanosine triphosphate; GAP: GTPase activating protein; GDP: Guanosine diphosphate; GEF: Guanine nucleotide exchange factor; KRAS: Kirsten rat sarcoma virus.

BI-3406 inhibits the interaction between KRAS and SOS1 which has been shown to cause tumor regression in KRAS-driven cancer cell models. Synergy was observed with SOS1/MEK inhibitors as this combination can counteract adaptive resistance to MEK inhibitors[20]. ERAS-601 is a small molecule allosteric inhibitor of SHP2 that stops KRAS from cycling into its GTP-active state, which inhibits cellular proliferation in multiple $KRAS^{G12C}$ mutated tumor cell models[21]. Recently the Food and Drug Administration (FDA) granted fast track designation to BBP-398 (SHP2 inhibitor) in combination with Sotorasib for $KRAS^{G12C}$-mutated metastatic non-small-cell lung carcinoma (NSCLC). There is an ongoing trial to evaluate the safety and efficacy of this combination [national clinical trial (NCT) 05480865]. Combination of $KRAS^{G12C}$ inhibitor (JAB-21822) and SHP2 inhibitor (JAB-3312) showed synergistic effect in $KRAS^{G12C}$-resistant tumor cells[22], currently in phase I/II trial for PDAC (NCT05288205).

MAPK/ERK pathway

The MAPK/ERK pathway was shown in Table 1.

KRAS

Direct inhibition of the KRAS protein remains a challenge, due to its small size of 21 kDa and the lack of hydrophobic pockets on its surface. Those pockets, if found, can then be blocked by small molecules and ultimately disrupt its interaction with other proteins[23]. Several attempts have been made to directly target KRAS, but results were non-

Table 1 Kirsten rat sarcoma virus-rapidly accelerated fibrosarcoma-mitogen-activated protein kinase/extracellular regulated protein kinases-extracellular regulated protein kinases pathway inhibitors

Agent	FDA approved[1]	Clinical trials[2]		
		Conditions (phase)	Combination	NCT number
SOS inhibitors				
BI-1701963	N/A	Advanced solid tumors (I); advanced solid tumors (I); metastatic colorectal cancer (I)	Trametinib; BI 3011441; irinotecan	NCT04111458; NCT04835714; NCT04627142
SHP2 inhibitors				
ERAS-601	N/A	Advanced/ metastatic solid tumors (I)	Cetuximab, pembrolizumab	NCT04670679
JAB-3312	N/A	Advanced solid tumors (I); advanced solid tumors (I/II)	N/A; binimetinib, pembrolizumab, sotorasib, osimertinib	NCT04045496; NCT04720976
BBP-398 (IACS-15509)	(+ sotorasib) fast track designation for metastatic NSCLC	Advanced solid tumor (I); advanced NSCLC (I); advanced solid tumors (I); advanced solid tumors (I)	N/A; nivolumab; N/A; sotorasib	NCT05621525; NCT05375084; NCT04528836; NCT05480865
RLY-1971	N/A	Advanced/metastatic solid tumors (I)	N/A	NCT04252339
TNO155	N/A	Advanced solid tumors (I); advanced solid tumors (I)	EGF816 (nazartinib); spartalizumab, ribociclib	NCT03114319; NCT04000529
RMC-4630	N/A	Relapsed/refractory solid tumors (I); NSCLC (II); metastatic KRAS mutant cancers (I); relapsed/refractory solid tumors, locally advanced/metastatic EGFR positive NSCLC (I/II)	N/A; sotorasib LY3214996; cobimetinib, osimertinib	NCT03634982; NCT05054725; NCT04916236; NCT03989115
Direct KRAS inhibitors				
G12C				
Sotorasib (AMG 510, Lumakras)	Advanced NSCLC	Colorectal cancer (III); advanced solid tumors (Ib/II)	Panitumumab; N/A	NCT05198934; NCT04185883
Adagrasib (MRTX849, Krazati)	Locally advanced or metastatic NSCLC	Metastatic PC (Ib); colorectal cancer (I); solid tumors (I/II); advanced solid tumors (I); advanced/metastatic cancers (I/II)	N/A; cetuximab and irinotecan; N/A; BI-1701963; TNO155	NCT05634525; NCT05722327; NCT05162443; NCT04975256; NCT04330664
JNJ-74699157	N/A	Advanced solid tumors (I)	N/A	NCT04006301
LY3499446	N/A	Advanced solid tumors (I/II)	Abemaciclib, cetuximab, erlotinib, docetaxel	NCT04165031
GDC 6036	N/A	Advanced/metastatic solid tumors (I)	Atezolizumab, cetuximab, bevacizumab, erlotinib, GDC-1971, inavolisib	NCT04449874
D-1553	N/A	Advanced/metastatic solid tumors (I/II); NSCLC (I/II)	N/A; N/A	NCT04585035; NCT05383898
G12D				
MRTX1133	N/A	Pancreatic, lung, and colorectal cancers (I/II)	N/A	Enters phase I in 2023
Tricomplex inhibitors				
RMC-6236	N/A	Advanced solid tumors (I)	N/A	NCT05379985
RMC-6291	N/A	Advanced solid tumors (I)	N/A	NCT05462717
RAF inhibitors				
Sorafenib (BAY43-9006, NEXAVAR)	Unresectable HCC; advanced RCC; thyroid cancer	PC that cannot be removed by surgery (II); unresectable PC (I); metastatic PC (II)	Erlotinib; gemcitabine, sorafenib and radiotherapy; alone or with gemcitabine	NCT00837876; NCT00375310; NCT00114244
Vemurafenib (PLX4032, RG7204,	BRAF V600E melanoma, ECD	PC (II)	Sorafenib	NCT05068752

RO5185426, ZELBORAF)				
Dabrafenib (GSK2118436, TAFINLAR)	(+ Trametinib) BRAF V600E or V600K melanoma, NSCLC, anaplastic thyroid cancer, solid tumors	Colorectal cancer (II); advanced/metastatic BRAF V600 colorectal cancer (I)	Trametinib + PDR001; trametinib, LTT462, LXH254, TNO155, spartalizumab, tislelizumab	NCT03668431; NCT04294160
Encorafenib (BRAFTOVI)	BRAF V600E metastatic colorectal cancer	Localized colon or upper rectum cancer with BRAF V600E mutation (II)	Cetuximab	NCT05706779
Regorafenib (BAY 73-4506, STIVARGA)	Metastatic colorectal cancer; advanced GIST	Solid tumors (II)	Nivolumab	NCT04704154
Lifirafeni (BGB-283)	N/A	Advanced or refractory solid tumors (I/II)	Mirdametinib	NCT03905148
Paradox breakers				
PLX7904/ PLX8394 (PB04)	N/A	Advanced cancers (I/IIa)	N/A	NCT02012231
Pan-RAF inhibitors				
LY3009120	N/A	Advanced cancer (I)	N/A	NCT02014116
MLN2480 (BIIB-024, TAK580, Tovorafenib)	N/A	Relapsed or refractory solid tumors followed by a dose expansion in participants with metastatic melanoma (I); advanced non-hematologic malignancies (I)	N/A; MLN0128 or alisertib, or paclitaxel, or cetuximab, or irinotecan	NCT01425008; NCT02327169
HM95573 (Belvarafenib)	N/A	Locally advanced or metastatic solid tumors (I)	Cobimetinib or cetuximab	NCT03284502
BMS-908662 (XL281)	N/A	Advanced or metastatic colorectal cancer (I/II); advanced solid tumors (I)	Alone or with cetuximab; N/A	NCT01086267; NCT00451880
MEK inhibitors				
Trametinib (GSK1120212, JTP-74057)	(+Dabrafenib) BRAF V600E or V600K melanoma, NSCLC, anaplastic thyroid cancer, solid tumors	Cancers with BRAF V600E mutations (II); solid tumors (I); PC (II); metastatic PC (II); biliary tract cancer (II)	Dabrafenib; gemcitabine; SBRT + pembrolizumab; gemcitabine; N/A	NCT04439292; NCT01428427; NCT02704156; NCT01231581; NCT01943864
Cobimetinib (XL-518, GDC-0973, RG7421, Cotellic)	Histiocytic neoplasms, melanoma	PC (I); locally advanced or metastatic PC (I)	N/A; calaspargase Pegol-mknl	NCT04005690; NCT05034627
Selumetinib (AZD6244, ARRY-142886, Koselugo)	Pediatric neurofibromatosis type 1	Advanced or metastatic PC who have failed first line gemcitabine (II); locally advanced or metastatic pancreatic cancer with KRAS G12R mutations (II); metastatic pancreatic cancer previously treated with chemotherapy (II); locally advanced or metastatic PC (II)	N/A; N/A; MK2206 (Akt inhibitor) or mFOLFOX; erlotinib hydrochloride	NCT00372944; NCT03040986; NCT01658943; NCT01222689
Binimetinib (ARRY-438162, ARRY-162, MEK162, MektoviI)	Unresectable or metastatic melanoma with a BRAF V600E mutation	Advanced BRAF mutant cancers (I/II); PC with somatic BRAF V600E mutation (II); advanced solid tumors harboring RAS or BRAFV60330E mutations (I)	Encorafenib; Encorafenib; RAF 265	NCT03843775; NCT04390243; NCT01352273
Pimasertib (AS703026, SAR24550, EMD1036239, MSC1936369B)	N/A	PC (I/II)	Gemcitabine	NCT01016483
Refametinib (RDEA119, BAY86-9766)	N/A	Advanced or metastatic cancer (I); RAS-mutant hepatocellular carcinoma (II); advanced cancer (Ib)	Regorafenib; N/A; copanlisib	NCT02168777; NCT01915589; NCT01392521
E6201 (ER 806201)	N/A	BRAF V600 mutated metastatic melanoma (I); advanced solid tumors (I)	Dabrafenib; N/A	NCT05388877; NCT00794781
PD-0325901 (Mirdametinib)	N/A	Advanced cancer (I)	PF-05212384 or Irinotecan	NCT01347866
AZD8330 (ARRY-424704, ARRY-704)	N/A	Advanced malignancies (I)	N/A	NCT00454090
GDC-0623 (RG7420, G-868)	N/A	Locally advanced or metastatic solid tumors (I)	N/A	NCT01106599

RO4987655 (CH4987655, RG7167)	N/A	Advanced solid tumors (I)	N/A	NCT00817518
RO5126766 (CH5126766, RG7304)	N/A	Advanced solid tumors (I)	N/A	NCT00773526
TAK733	N/A	Advanced nonhematologic malignancies (I)	N/A	NCT00948467
ERK inhibitors				
Ulixertinib (BVD-523)	N/A	Advanced pancreatic and other solid tumors (I); metastatic PC (I); advanced MAPK pathway-altered malignancies	Palbociclib; Nab-paclitaxel and gemcitabine; N/A	NCT03454035; NCT02608229; NCT04566393
GDC-0994 (RG7842)	N/A	Locally advanced or metastatic solid tumors (I)	N/A	NCT01875705
MK-8353 (SCH900353)	N/A	Advanced/metastatic solid tumors (I); advanced malignancies (I)	Selumetinib; pembrolizumab	NCT03745989; NCT02972034
JSI-1187	N/A	Advanced solid tumors with MAPK pathway mutations (I)	Alone or with dabrafenib	NCT04418167
ERAS-007	N/A	Advanced or metastatic solid tumors (I/II); advanced gastrointestinal malignancies (I/II)	ERAS-601; encorafenib, cetuximab, palbociclib	NCT04866134; NCT05039177
Menin inhibitor				
BMF-219	N/A	NSCLC, pancreatic, colorectal cancers (I)	N/A	NCT05631574

[1]www.fda.gov.
[2]clinicaltrials.gov.
FDA: Food and Drug Administration; SOS: Son of Sevenless; KRAS: Kirsten rat sarcoma virus; HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma; ECD: Erdheim-Chester disease; GIST: Gastrointestinal stroma tumors; PC: Pancreatic cancer; RAF: Rapidly accelerated fibrosarcoma; RAS: Rat sarcoma viral oncogene family; MAPK: Mitogen-activated protein kinases; NSCLC: Non-small-cell lung carcinoma; SHP2: Src homology-2 domain-containing protein tyrosine phosphatase-2; NCT: National clinical trial; MEK: Mitogen-activated protein kinase/extracellular regulated protein kinases; N/A: Not applicable.

satisfactory[24-26]. Only recently AMG 510 (sotorasib) was developed to target G12C mutation in NSCLC without inhibiting wild-type *KRAS*[27]. Adagrasib (MRTX849) which is also a $KRAS^{G12C}$ inhibitor is well tolerated, and preliminary results showed partial response in 50% of patients with PDAC harboring this mutation[28]. However, $KRAS^{G12C}$ only occurs in 1%-2% PC and attempts to target more common *KRAS* isoforms have failed. One promising compound is MRTX1133, a small molecule that selectively inhibits $KRAS^{G12D}$ by preventing SOS-catalyzed nucleotide exchange. Subsequently, it promotes tumor regression in immunocompetent PC models and alters the tumor microenvironment by increasing tumor associated macrophages (TAM) and tumor-infiltrating cytotoxic T-cells. MRTX1133 is expected to enter phase I trial in 2023[29,30]. Other agents inhibiting G12D in the pre-clinical phase include BI-KRASG12D, JAB-22000, and ERAS-4. A new category of drugs called tricomplex inhibitors has shown promising results in pre-clinical models of $KRAS^{G12V}$ mutant cancers[31] and in a phase I trial RMC-6236 in $KRAS^{G12}$-mutant advanced solid tumors excluding G12C (NCT05379985). A recent study was able to selectively target $KRAS^{G12R}$ using a small molecule electrophile[32]. Due to the challenging nature of direct KRAS inhibition focus was shifted on downstream signaling, knowing that some of the challenges include compensation by other pathways, and that inhibiting multiple pathways can result in toxicity[33].

Multiple mechanisms are implicated in the inevitable drug resistance seen with KRAS inhibitors, either by activation of wild-type KRAS which is mediated by receptor tyrosine kinase[34], synthesizing new $KRAS^{G12C}$ proteins in response to MAPK suppression[35], or developing secondary mutations in KRAS inhibitor binding pocket[36].

RAF

With regards to drugs targeting the MAPK pathway, sorafenib was the first RAF inhibitor to be FDA-approved, initially for advanced renal cell carcinoma, followed by unresectable/metastatic hepatocellular carcinoma and metastatic differentiated thyroid cancer[37]. In a phase II trial combining sorafenib and erlotinib, 12 of the first 15 patients required dose delays or reductions due to toxicity, and the study failed to reach its primary endpoint of 8-week progression-free survival (PFS)[38]. A second-generation of RAF inhibitors (*e.g.*, vemurafenib and dabrafenib) was proven to be effective in *BRAF V600E* mutant metastatic melanoma[39]. Dabrafenib in combination with trametinib received a tumor agnostic accelerated approval for treatment of unresectable/metastatic solid tumors with *BRAF V600E* mutation that progressed on prior treatment[40]. Unfortunately, vemurafenib and dabrafenib were not as effective in *KRAS*-mutant cancers, due to compensatory ERK activation that led to enhanced tumor growth[41,42]. A third generation of RAF inhibitors called "paradox breakers" (PLX7904 and PLX8394) also blocks MEK-ERK1/2, which can overcome this resistance mechanism [43], Unfortunately, a phase I/II trial to evaluate the safety of PLX8394 was terminated due to low accrual. Recently, another group called "pan-RAF inhibitors" (LY3009120, MLN2480, and HM95573) entered phase I trials. LY3009120 is a kinase inhibitor that showed efficacy in inhibiting mutated *KRAS* and *BRAF* in preclinical models of colorectal cancer

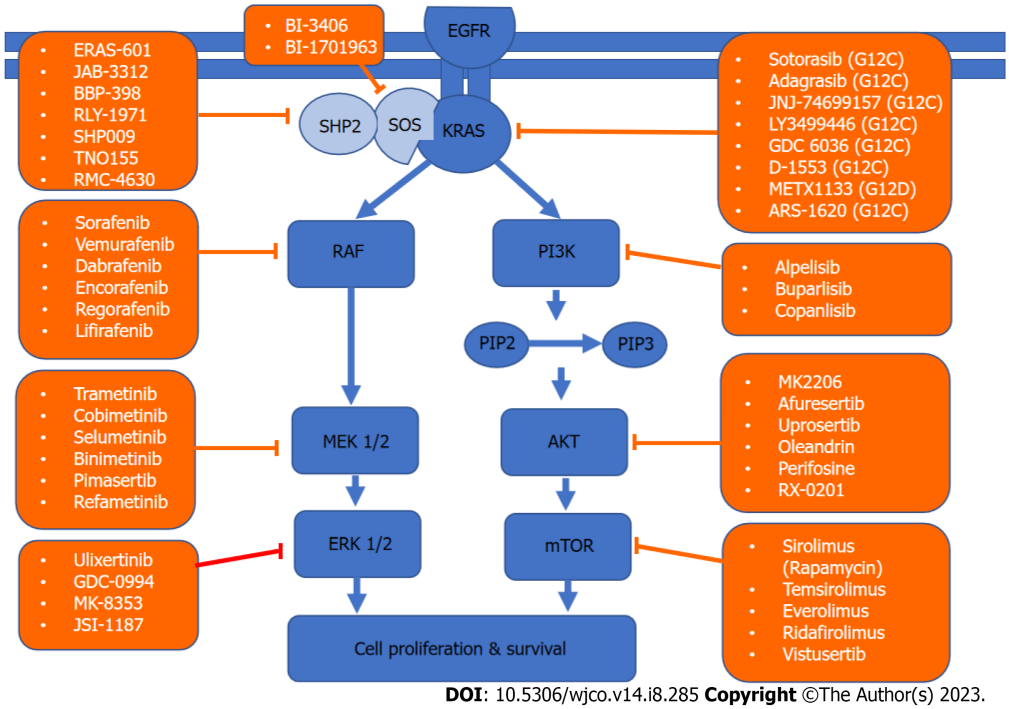

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Figure 3 Kirsten rat sarcoma virus signaling network and targeted therapy. A schematic of the two major Kirsten rat sarcoma virus pathways driving cell survival and drugs that target them. KRAS: Kirsten rat sarcoma virus; AKT: Protein kinase; EGFR: Epidermal growth factor receptor; PIP: Prolactin-induced protein; ERK: Extracellular regulated protein kinases; MEK: Mitogen-activated protein kinase/extracellular regulated protein kinases; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; RAF: Rapidly accelerated fibrosarcoma; SHP2: Src homology-2 domain-containing protein tyrosine phosphatase-2; SOS: Son of sevenless.

with minimal paradoxical MAPK activation[44,45], however, a phase I trial in advanced cancers was terminated early due to lack of sufficient clinical efficacy (NCT02014116). MLN2480 (tovorafenib) showed an acceptable safety profile[46], and HM95573 (belvarafenib) was well tolerated and showed anti-tumor activity in advanced solid tumors with RAS or RAF mutations[47]. The Yes-associated protein (YAP) is a transcription coregulator downstream from KRAS that promotes cell proliferation[48]. Combining LY3009120 and YAP-inhibitor (verteporfin) showed anti-tumor effect *in vivo* and *in vitro* by blocking compensatory activation of AKT pathway[49].

MEK

As mentioned above, trametinib is a MEK1/2 inhibitor FDA approved in combination with dabrafenib (RAF-inhibitor) as a tumor agnostic drug[50]. Trametinib was studied in combination with gemcitabine in a placebo controlled clinical trial for untreated metastatic PDAC. Unfortunately, it did not show improvement in overall survival (OS), PFS, or overall response rate (ORR)[51]. This is potentially due to a compensatory mechanism called autophagy, initiated through activation of the AKT pathway[52]. A Phase II trial of selumetinib (MEK1/2 kinase inhibitor) in PC did not show any significant difference in OS when compared to capecitabine[53], another phase II study of selumetinib targeting only PC patients with $KRAS^{G12R}$ mutation after at least two lines of prior systemic chemotherapy did not improve ORR, however, three patients had stable disease for ≥ 6 months[54]. A phase I/II trial studied the selective MEK1/2 inhibitor pimasertib in combination with gemcitabine *vs* gemcitabine alone in patients with metastatic PC. Despite the promising safety and efficacy of this combination, it did not improve PFS or OS[55]. Unfortunately, in whole there was no observed clinical benefit of MEK inhibitors in the multiple trials done in PC.

ERK

After resistance to BRAF and MEK inhibitors, the next downstream target is ERK. SCH772984[56] is a selective inhibitor of ERK1/2 that showed tumor regression in xenograft models refractory to BRAF and MEK inhibitors. Similar effects were seen with ulixertinib[57]. A phase Ib trial combining ERK1/2 inhibitor (GDC-0994) and MEK inhibitor (cobimetinib) in advanced solid tumors was terminated due to tolerability issues[58]. The ERK1/2 inhibitor JSI-1187-01 demonstrated pre-clinical efficacy in tumor models with MAPK pathway mutations, as well as synergy with BRAF inhibitors[59], and is being studied in a phase I trial (NCT04418167).

PI3K-AKT-mTOR-pathway

The PI3K-AKT-mTOR-pathway was shown in Table 2. One of the postulated reasons EGFR inhibitors and other targeted therapies develop resistance is the hyper-activation of PI3K-AKT-mTOR pathway, which can drive cancer progression and survival. PI3K is overexpressed in around 50% of patients with PC[60], and AKT2 is amplified in 10%-20% of PDAC [61]. TAM plays a role in the development of PC[62] by creating an immune-suppressive microenvironment, minimizing

Table 2 Phosphoinositide 3-kinase-protein kinase-mammalian target of rapamycin-pathway inhibitors

Agent	Combination	Phase	NCT number[1]
PI3K inhibitors (p110α) isoform			
Alpelisib (BYL719)	Gemcitabine and abraxane	I	NCT02155088
Buparlisib (BKM120)	mFOLFOX6; trametinib (MEKi)	I; I	NCT01571024; NCT01155453
Pan-PI3K inhibitors			
Copanlisib(BAY 80–6946)	N/A	I	NCT00962611
PI3K and mTOR inhibitors			
Voxtalisib (SAR245409, *XL765*)	N/A	I	NCT00485719
Dactolisib(NVP-BEZ235)	MEK162 (MEKi)	I	NCT01337765
Gedatolisib (PF-05212384, PKI-587)	Palbociclib (CDKi)	I	NCT03065062
Pan-Akt inhibitors			
MK2206	Monotherapy; dinaciclib (CDKi); selumitinib (MEKi) vs mFOLFOX6	I; I; II	NCT00848718; NCT01783171; NCT01658943
Afuresertib (GSK2110183)	Trametinib (MEKi); N/A	I; II	NCT01476137; NCT01531894
Uprosertib (GSK2141795)	Trametinib (MEKi)	I	NCT01138085
Oleandrin (PBI-05204)	N/A	II	NCT02329717
Perifosine	N/A	II; II	NCT00053924; NCT00059982
RX-0201	Gemcitabine	II	NCT01028495
Rapalogs (mTORC1 inhibitors)			
Sirolimus (rapamycin)	Sunitinib (RTKi); N/A; metformin; vismodegib (SMOi)	I; II; I/II; I	NCT00583063; NCT00499486; NCT02048384; NCT01537107
Temsirolimus (*CCI-779*, Torisel)	Lenalidomide; gemcitabine; nivolumab (PD-1i)	I; I; I/II	NCT01183663; NCT00593008; NCT02423954
Everolimus (RAD001)	Sorafenib (RTKi); trametinib (MEKi); gemcitabine; cetuximab (EGFRi) and capecitabine; N/A	I; I; I/II; I/II; II	NCT00981162; NCT00955773; NCT00560963; NCT01077986; NCT00409292
Ridafirolimus	Bevacizumab (VEGFRi)	I	NCT00781846
mTORC1/2 inhibitors			
Vistusertib (AZD2014)	N/A; selumitinib (MEKi); olaparib (PARPi)	I; II; II	NCT01026402; NCT02583542; NCT02576444

[1]clinicaltrials.gov

PI3K: Phosphoinositide 3-kinase; NCT: National clinical trial; MEKi: Mitogen-activated protein kinase/ extracellular regulated protein kinases inhibitor; CDKi: Cyclin-dependent kinase inhibitor; RTKi: Receptor tyrosine kinase inhibitor; SMOi: Smoothened inhibitor; PD-1i: Programmed cell death receptor-1 inhibitor; EGFRi: Epidermal growth factor receptor inhibitor; VEGFRi: Vascular endothelial growth factor receptor inhibitor; mTOR: mammalian target of rapamycin; PARPi: Poly (ADP-ribose) polymerase inhibitor; N/A: Not applicable.

the antitumor effect of T-cells[63]. PI3K helps drive this immune suppression, so its inhibition can restore immune response against cancer cells as well as potentiate the effect of chemotherapy[64]. Additionally, AKT mediates an anti-apoptotic effect and plays a role in chemoresistance[65]. Phosphatase and tensin homolog is a tumor suppressor of the AKT/mTOR pathway, its loss has been implicated in PC development, recurrence, and prognosis[66], as well as acceleration of *KRAS*^{G12D}-induced PDAC in mice[67]. An *in vivo* study tested PI3Kα-specific inhibitor (BYL) in combination with an EGFR inhibitor (erlotinib) and showed reduced tumor volume and apoptosis in PDAC cell lines[68]. Currently a clinical trial combining gedatolisib (PI3K/mTOR inhibitor) with palbociclib (CDK4/6 inhibitor) in advanced squamous cell cancers of the lung, pancreas, and solid tumors is recruiting (NCT03065062). A phase I/II trial studied the safety and efficacy of combining everolimus (mTOR inhibitor), cetuximab (EGFR inhibitor), and capecitabine, however, the combination resulted in significant epidermal and mucosal toxicities with minimal efficacy[69].

Small interfering RNA, MicroRNA, and clustered regularly interspaced short palindromic repeats

Pre-clinical studies show that small interfering RNAs (siRNAs) have potential in cancer treatment. To deliver siRNAs to target cancer cells, scientists devised two unique methods, one utilized nanoparticle[70] to target lung cancer cells and another study used a biodegradable polymeric matrix (LODER) to carry the anti *KRAS*^{G12D} siRNA. This resulted in the

decrease of KRAS levels and inhibited cell proliferation[71]. MicroRNAs (miRNA) regulate cell proliferation and contribute to PC development. Depending on their role they can act as tumour suppressor or oncogenic miRNAs[72,73]. MRX34 (miRNA-34 mimic) was used in a phase I clinical trial that utilized lipid-based vesicles (NOV40) as a delivery vector, for treating patients with advanced solid tumors. miRNA-96 directly targets *KRAS* oncogene decreasing PC cell invasion and slowing tumor growth both *in vivo* and *in vitro*[74]. Clustered regularly interspaced short palindromic repeat (CRISPR) is currently being studied in *KRAS*-mutated cancers. This technology is being harnessed to target inactivated tumor suppressor genes or overactive oncogenes. In a 2018 study CRISPR-Cas13a was developed to target $KRAS^{G12D}$ mRNA. Subsequently, it also suppressed downstream ERK and AKT proteins resulting in apoptosis and significant tumor suppression *in vivo* and *in vitro*[75]. Two phase I trials utilizing the CRISPR platform are currently ongoing in PC (NCT04426669 and NCT04842812).

CONCLUSION

KRAS mutation remains the hallmark genetic aberration leading to PC. Although several studies have demonstrated positive preclinical results, the resulting clinical trial results have been largely disappointing. As we continue to have a deeper understanding of the KRAS pathway, resistance mechanisms, and the role and function of the immune system; we get closer to developing effective therapies to outsmart the scourge that is PC. Ongoing clinical trials targeting more common *KRAS* mutations in PC will hopefully lead to more effective therapy and change the outcomes for the thousands of patients affected by this disease every year.

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FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Immune responses of six-transmembrane epithelial antigen of the prostate 4 functions as a novel biomarker in gastric cancer

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Abstract

BACKGROUND

Immune cells play an important role in regulating the behavior of tumor cells. According to emerging evidence, six-transmembrane epithelial antigen of the prostate 4 (STEAP4) performs a crucial part in tumor microenvironmental immune response and tumorigenesis, and serves as the potential target for cellular and antibody immunotherapy. However, the immunotherapeutic role of STEAP4 in gastric cancer (GC) remains unclear.

AIM

To investigate the expression of STEAP4 in GC and its relationship with immune infiltrating cells, and explore the potential value of STEAP4 as an immune prognostic indicator in GC.

METHODS

The expression level of STEAP4 was characterized by immunohistochemistry in tumors and adjacent non-cancerous samples in 96 GC patients. Tumor Immune Estimation Resource was used to study the correlation between STEAP4 and tumor immune infiltration level and immune infiltration gene signature. R package was used to analyze the relationship between STEAP4 expression and immune and stromal scores in GC (GSE62254) by the ESTIMATE algorithm, and Kaplan-Meier Plotter and Gene Expression Profiling Interactive Analysis were applied to analyze the effect of STEAP4 on clinical prognosis.

RESULTS

Immunohistochemistry analysis showed that STEAP4 expression was higher in

GC tissues than in adjacent tissues, and STEAP4 expression was positively correlated with the clinical stage of GC. In GC, the expression of STEAP4 was positively correlated with the infiltration levels of B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells. The expression level of STEAP4 was strongly correlated with most of the immune markers. In addition, STEAP4 expression was inversely correlated with tumor purity, but correlated with stromal score ($r = 0.43$, $P < 0.001$), immune score ($r = 0.29$, $P < 0.001$) and estimate score ($r = 0.39$, $P < 0.001$). Moreover, stromal, immune, and estimate scores were higher in the STEAP4 high expression group, whereas tumor purity was higher in the STEAP4 Low expression group. The relationship between STEAP4 expression and prognosis of patients with GC was further investigated, and the results showed that high STEAP4 expression was associated with poor overall survival and disease-free survival. In addition, Kaplan-Meier Plotter showed that high expression of STEAP4 was significantly correlated with poor survival of patients with GC.

CONCLUSION

The current findings suggest an oncogenic role for STEAP4 in GC, with significantly high levels being associated with poor prognosis. Investigation of the GC tumor microenvironment suggests the potential function of STEAP4 is connected with the infiltration of diverse immune cells, which may contribute to the regulation of the tumor microenvironment. In conclusion, STEAP4 may serve as a potential therapeutic target for GC to improve the immune infiltration, as well as serve as a prognostic biomarker for judging the prognosis and immune infiltration status of GC.

Key Words: Six-transmembrane epithelial antigen of the prostate 4; Gastric cancer; Immune infiltration; Prognosis; Biomarker

Core Tip: The present study analyzed the expression level of six-transmembrane epithelial antigen of the prostate 4 (STEAP4) in gastric cancer (GC) and found that high STEAP4 expression is significantly associated with poor survival of patients. STEAP4 is positively correlated with immune infiltration of different types of immune cells, and has strong correlations with most immune markers. STEAP4 may become a potential biomarker for predicting the prognosis of GC patients.

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INTRODUCTION

Gastric cancer (GC), the fifth most common malignant tumor, is the second leading cause of cancer-related death worldwide[1,2]. Although the overall survival (OS) of GC patients has improved with standardized extended (D2) lymphadenectomy and the implementation of chemotherapy and targeted therapy, its survival rate is still less than 30% [3,4]. However, recent studies have shown that immune-involved mechanisms play a certain critical role in gastric tumors, and immunotherapy is considered a promising strategy for the therapeutics of gastric tumors[5]. In addition, Zhang *et al*[6] found that tumor-infiltrating lymphocytes can affect the prognosis and efficacy of chemotherapy and immunotherapy in GC patients. Therefore, there is an urgent need to elucidate the mechanism of tumor-immune interaction in GC, and to identify novel prognostic targets for immunotherapy.

Six-transmembrane epithelial antigen of the prostate 4 (STEAP4) consists of an N-terminal oxidoreductase domain and a six-helix transmembrane domain, serving as a transmembrane protein involved in metal reductase transport of copper and iron[7,8]. It is reported that high expression of STEAP4 is correlated with the pathogenesis of cancer and metabolic diseases[9-11]. STEAP4 is not only involved in the occurrence and development of breast cancer[12,13], but is also related to the inflammatory response of colon cancer[14]. It is also found that STEAP4 is highly expressed in prostate cancer tissues, serving as a promising prognostic indicator[15]. Nevertheless, the effect of STEAP4 in GC development and the mechanisms involved remain unclear.

In this study, the expression of STEAP4 and its correlation with the prognosis of GC patients are comprehensively analyzed. Moreover, the relevance between STEAP4 and different tumor-infiltrating immune cells and immune cell markers is also examined to clarify the essential role of STEAP4 in GC and provide a potential relationship and mechanism between STEAP4 and tumor-immune interactions.

MATERIALS AND METHODS

Patient information and ethics statement

Tissue array (XT17-037, OUTDO, China) recruited total 96 cases of GC, including 84 pairs of GC tissues and corresponding adjacent tissues, and 12 extra GC samples. This investigation of STEAP4 in GC was approved by the Ethics Committee of Shantou University Medical College.

Immunohistochemical staining

The protocol for immunohistochemical staining was conducted as described previously[16]. The primary antibody used was anti-STEAP4 antibody in 1:400 diluent (Proteintech 11944-AP). The sections were visualized and evaluated independently under a bright-field microscope (PerkinElmer Vectra, United States) by two investigators with no prior knowledge of the patient information. The evaluation of STEAP4 expression was based on the sum of the scores from the staining intensities (0-3 indicating colorless, light yellow, brown and dark) and the percentage of positive cells (0-4 for 0%, 1% to 25%, 26% to 50%, 51% to 74%, and 76% to 100%), and the patients were divided into two groups based on the sum score results[17].

STEAP4 mRNA expression in GC

Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/index.html), an interactive network from TCGA and GTEx projects was used to further analyze the expression level of STEAP4, in TCGA expression data, in different clinical stages of GC[18]. The survival information of GC patients was also evaluated based on STEAP4 expression in the GEPIA datasets.

Relationship between STEAP4 and infiltrating immune cells in GC

Tumor Immune Estimation Resource (TIMER) (https://cistrome.shinyapps.io/timer/) is an online dataset for systematic analysis of immune infiltration in various types of cancer[19]. The correlation between STEAP4 level and the abundance of infiltrating immune cells was analyzed using gene modules in the database. In addition, the correlation between STEAP4 level and biomarkers of tumor-infiltrating immune cells was also investigated, with scatterplots and Spearman's value for estimated statistical signifcance. Gene markers of tumor-infiltrating immune cells included CD8+ T cells, CD4+T cells, B cells, monocytes, TAMs, M1 macrophages, M2 macrophages, neutrophils, natural killer cells (NK), dendritic cells (DCs), T-helper 1 (Th1) cells, T-helper 2 (Th2) cells, and follicle-helper T (Tfh) cells, T-helper 17 (Th17) cells, Tregs and exhausted T cells[20-22].

Expression of infiltrating immune cells in GC

The "ESTIMATE" algorithm of R package was used to calculate the immune score and stromal score of the GSE62254 dataset (n = 300), which was helpful for the evaluation of immune and stromal constitute in tumors. The immune and stromal scores were also calculated by STEAP4 expression in immune and stromal cells in GC.

The prognostic value of STEAP4 in GC

Kaplan-Meier Plotter (http://kmplot.com/analysis/) was applied to analyze the correlation between STEAP4 and survival rate of GC[23]. Hazard ratios (HRs) and log-rank P values for 95% confidence intervals were calculated simultaneously.

Statistical and survival analysis

SPSS software was used for χ^2 or Fisher's exact probability tests to analyze the relationship of STEAP4 level and clinic information of GC patients. To investigate the prognosis of GC patients, the Kaplan-Meier survival curve was conducted, along with log-rank test. Differences were achieved with $P < 0.05$.

RESULTS

STEAP4 is highly expressed in GC compared with adjacent normal tissues

To investigate the expression profiling of STEAP4 in GC tissues, cancerous tissues and adjacent normal tissues were obtained from GC patients. Representative images of STEAP4 expression are shown in Figure 1. Based on the quantitation of STEAP4 expression levels in GC, a significantly high level of STEAP4 in GC tissues was found, compared with corresponding adjacent normal tissues (P = 0.0056) (Table 1).

A high level of STEAP4 tends to contribute to GC progression

The expression level of STEAP4 in 96 GC patients was further analyzed with their clinicopathological parameters (Table 2). Although no statistical significance was found between the expression level of STEAP4 and the clinicopathologic parameters, including age of diagnosis, gender, lymph node status, vascular invasion and clinical stage ($P > 0.05$), the proportion of patients with high STEAP4 expression tended to increase with the progression of pathological stage, and high STEAP4 expression tended to be associated with lymph node metastasis and vascular invasion, indicating the potential contribution of STEAP4 to the progression of GC. The GEPIA database, regarding mRNA expression, was used

Table 1 Comparison of six-transmembrane epithelial antigen of the prostate 4 levels between gastric cancer and adjacent normal tissues

	Case (*n*)	STEAP4		χ^2	*P* value
		Low (%)	High (%)		
Tumor	84	20 (23.81)	64 (76.19)	7.674	0.0056
Normal	84	37 (44.05)	47 (55.95)		

STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

Table 2 Correlation between six-transmembrane epithelial antigen of the prostate 4 expression and clinicopathological parameters in gastric cancer patients

Clinical parameters	STEAP4		*P* value
	Low (%)	High (%)	
Age			
< 60	9 (25.0)	27 (75.0)	0.5662
≥ 60	12 (20.0)	48 (80.0)	
Gender			
Female	6 (19.4)	25 (80.6)	0.6800
Male	15 (23.1)	50 (76.9)	
T			
T1-3	15 (23.8)	48 (76.2)	0.5264
T4	6 (18.2)	27 (81.8)	
N			
N0	7 (35.0)	13 (65.0)	0.1105
N1-N3	14 (18.4)	62 (81.8)	
M			
M0	21 (22.3)	73 (77.7)	0.9999
M1	0 (0)	2 (100)	
Vascular invasion			
No	18 (26.1)	51 (73.9)	0.1105
Yes	3 (11.1)	24 (88.9)	
Clinical stage			
Phase 1	2 (25.0)	6 (75.0)	0.5900
Phase 2	8 (29.6)	19 (70.4)	
Phase 3	11 (18.6)	48 (81.4)	
Phase 4	0 (0)	2 (100)	

STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

to verify the relationship of STEAP4 with clinical stage of GC. Interestingly, there was no significant difference in the expression of STEAP4 between 4 different clinical stages. However, an increased expression of STEAP4 was found in Stage III and Stage IV, compared with Stage I and Stage II, predicting the potential promoting role of STEAP4 in GC (Figure 2).

STEAP4 is positively correlated with the extent of immune infiltration in GC

Considering that tumor purity is an important factor affecting immune infiltration of clinical tumor samples analyzed by genomic approaches[24], it is of interest to investigate the tumor microenvironment-related immune infiltration with

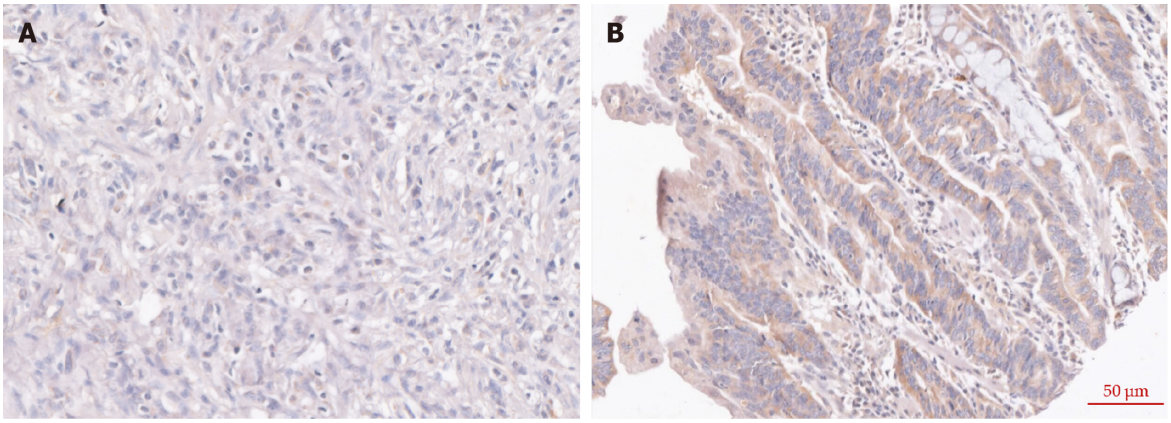

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Figure 1 Representative images of six-transmembrane epithelial antigen of the prostate 4 expression in patients with gastric cancer. A: Low expression of six-transmembrane epithelial antigen of the prostate 4 (STEAP4); B: High expression of STEAP4.

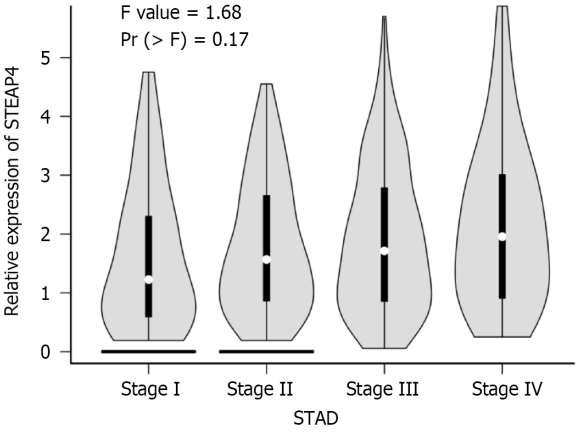

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Figure 2 Relationship between six-transmembrane epithelial antigen of the prostate 4 level and clinical stage of gastric cancer patients. STAD: Stomach adenocarcinoma; STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

STEAP4 levels. Interestingly, STEAP4 expression levels were found to be associated with higher immune infiltration in GC. The level of STEAP4 expression was positively associated with that of immune-infiltrating cells, including B cells, CD4+ T cells, neutrophils, macrophages and dendritic cells (Figure 3).

External verification confirms the positive correlation of STEAP4 with immune infiltration in GC

External verification was conducted on the GSE62254 dataset, with 300 GC samples, using the ESTIMATE algorithm in R software. Based on the features, stromal and immune scores were generated to reflect the proportion of stroma and immune cells, respectively, and single sample gene set enrichment analysis was used to combine the two to measure tumor purity. In Figure 4A-D, it is revealed that STEAP4 expression was inversely correlated with tumor purity and stromal score (r = 0.43, P < 0.001), immune score (r = 0.29, P < 0.001) and ESTIMATE score (r = 0.39, P < 0.001). In addition, stromal, immune, and estimate scores all increased with high STEAP4 expression (Figure 4F-H), whereas tumor purity was accompanied by low STEAP4 expression (Figure 4E).

Correlation analysis between STEAP4 expression and immunomarker sets

Due to the positive correlation between STEAP4 and immune infiltration was found in GC, further investigation was conducted to uncover the role of STEAP4 in the development of GC, and specify the subtype of immune cells associated with STEAP4. Diverse immunomarker sets were analyzed in TIMER database to verify the relationship of STEAP4 level with immune-infiltrating cells. After adjustment for purity, STEAP4 expression levels were significantly correlated with most of the immune marker sets of various immune cells and different T cells (Table 3).

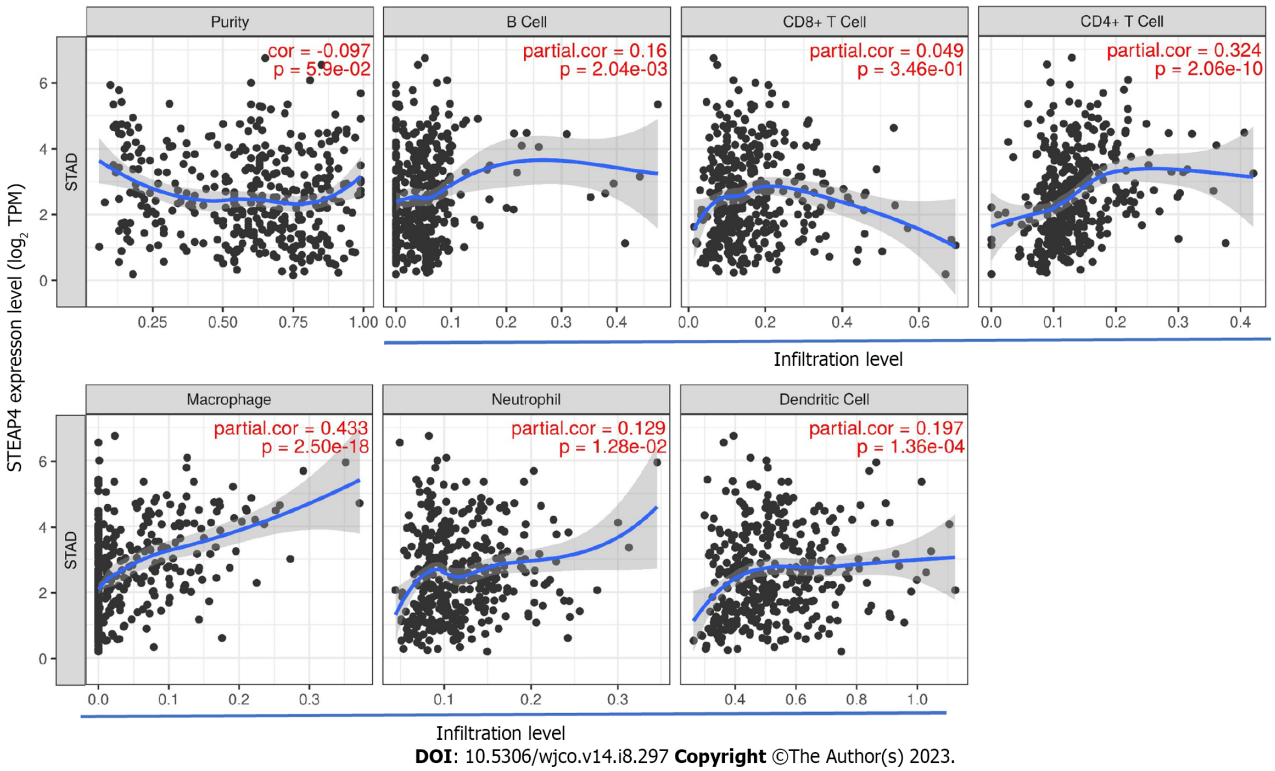
Interestingly, the expression levels of gene markers for B cells, monocytes, TAMs, M1 and M2 macrophages and other immune cells were correlated with the expression of STEAP4. Specifically, it was found that the expression level of CD19, B cell CD79A, CD86, monocyte CD115, TAM CCL2 and IL-10, M1 macrophage IRF5 and PTGS2, and M2 macrophage CD163, VSIG4, and MS4A4A were significantly correlated with STEAP4 expression (P < 0.01) (Table 3, Figure 5), suggesting a function of STEAP4 in regulating the infiltration of macrophages during the progression of GC.

Table 3 Correlation analysis between six-transmembrane epithelial antigen of the prostate 4 and the immunomarkers in gastric cancer

Immune cells	Gene markers	STAD			
		None		Tumor purity	
		Cor	*P* value	Cor	*P* value
CD8+ T cells	CD8A	0.083	0.0925	0.039	0.455
	CD8B	0.039	0.427	0.012	0.823
CD4+ T cells	CD3D	0.003	0.959	-0.059	0.254
	CD3E	0.043	0.382	-0.022	0.670
	CD2	0.048	0.325	-0.006	0.914
B cells	CD19	0.152	$P < 0.01$	0.127	$P < 0.05$
	CD79A	0.185	$P < 0.001$	0.148	$P < 0.01$
Monocytes	CD86	0.153	$P < 0.01$	0.109	$P < 0.05$
	CD115 (CSF1R)	0.298	$P < 0.001$	0.261	$P < 0.001$
TAMs	CCL2	0.334	$P < 0.001$	0.296	$P < 0.001$
	CD68	0.118	$P < 0.05$	0.085	0.0981
	IL10	0.250	$P < 0.001$	0.217	$P < 0.001$
M1 macrophages	INOS (NOS2)	-0.113	$P < 0.05$	-0.142	$P < 0.01$
	IRF5	0.220	$P < 0.001$	0.201	$P < 0.001$
	COX2 (PTGS2)	0.325	$P < 0.001$	0.312	$P < 0.001$
M2 macrophages	CD163	0.283	$P < 0.001$	0.248	$P < 0.001$
	VSIG4	0.232	$P < 0.001$	0.203	$P < 0.001$
	MS4A4A	0.479	$P < 0.001$	0.194	0.0999
Neutrophils	CD66b (CEACAM8)	-0.109	0.338	-0.089	0.452
	CD11b (ITGAM)	0.407	$P < 0.001$	0.118	0.320
	CCR7	0.384	$P < 0.001$	0.118	0.319
Natural killer cells	KIR2DL1	0.087	0.0768	0.078	0.129
	KIR2DL3	0.055	0.262	0.042	0.410
	KIR2DL4	-0.065	0.184	-0.088	0.087
	KIR3DL1	0.079	0.107	0.084	0.102
	KIR3DL2	0.073	0.138	0.063	0.217
	KIR3DL3	-0.071	0.148	-0.06	0.240
	KIR2DS4	0.019	0.693	0.012	0.819
Dendritic cells	HLA-DPB1	0.129	$P < 0.01$	0.08	0.120
	HLA-DQB1	0.025	0.609	-0.032	0.532
	HLA-DRA	0.086	0.0789	0.046	0.376
	HLA-DPA1	0.108	$P < 0.05$	0.066	0.199
	BDCA-1 (CD1C)	0.370	$P < 0.001$	0.351	$P < 0.001$
	BDCA-4 (NRP1)	0.533	$P < 0.001$	0.504	$P < 0.001$
	CD11c (ITGAX)	0.258	$P < 0.001$	0.217	$P < 0.001$
Th1	T-bet (TBX21)	0.050	0.307	0.008	0.881
	STAT4	0.204	$P < 0.001$	0.172	$P < 0.001$
	STAT1	-0.051	0.304	-0.070	0.174
	IFN-γ (IFNG)	-0.195	$P < 0.001$	-0.229	$P < 0.001$

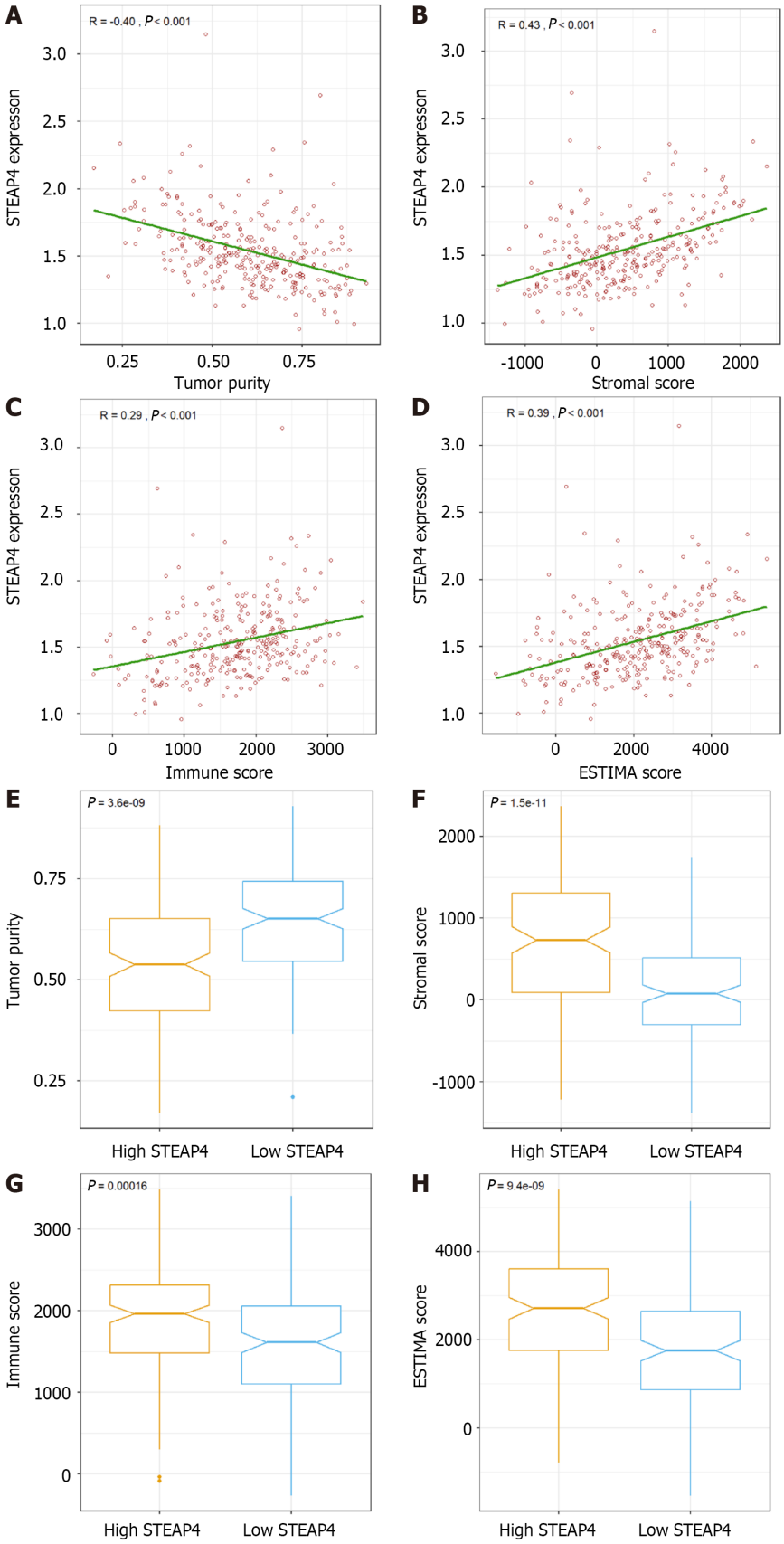
	IFN-α (TNF)	0.005	0.921	-0.045	0.387
Th2	GATA3	0.230	$P < 0.001$	0.205	$P < 0.001$
	STAT6	0.122	$P < 0.01$	0.119	$P < 0.05$
	STAT5A	0.220	$P < 0.001$	0.184	$P < 0.001$
	IL13	0.038	0.436	0.049	0.339
Tfh	BCL6	0.470	$P < 0.001$	0.451	$P < 0.001$
	IL21	-0.031	0.529	-0.055	0.285
Th17	STAT3	0.337	$P < 0.001$	0.310	$P < 0.001$
	IL17A	-0.268	$P < 0.001$	-0.278	$P < 0.001$
Treg	FOXP3	0.025	0.616	-0.028	0.589
	CCR8	0.158	$P < 0.01$	0.129	$P < 0.05$
	STAT5B	0.414	$P < 0.001$	0.383	$P < 0.001$
	TGFβ (TGFB1)	0.299	$P < 0.001$	0.266	$P < 0.001$
T cell exhaustion	PD-1 (PDCD1)	-0.060	0.221	-0.114	$P < 0.05$
	CTLA4	-0.072	0.141	-0.125	$P < 0.05$
	LAG3	-0.119	$P < 0.01$	-0.170	$P < 0.001$
	TIM-3 (HAVCR2)	0.124	$P < 0.05$	0.082	0.112
	GZMB	-0.121	$P < 0.01$	-0.169	$P < 0.001$

STAD: Stomach adenocarcinoma; TAM: Tumor-associated macrophage; Th: T helper cell; Tfh: Follicular helper T cell; Treg: Regulatory T cell; Cor: R value of Spearman's correlation; None: Correlation without adjustment. Tumor purity: Correlation adjusted by tumor purity.



DOI: 10.5306/wjco.v14.i8.297

Figure 3 Correlation of six-transmembrane epithelial antigen of the prostate 4 expression with immune infiltration level in gastric cancer.
STAD: Stomach adenocarcinoma.



DOI: 10.5306/wjco.v14.i8.297

Figure 4 Stromal and immune scores in relation to six-transmembrane epithelial antigen of the prostate 4 in gastric cancer. A: Tumor purity; B: Stromal score; C: Immune score; D: ESTIMATE score; E: Tumor purity was higher in the six-transmembrane epithelial antigen of the prostate 4 (STEAP4) low expression group; F-H: Stromal score, immune score and ESTIMATE score were higher in the STEAP4 high expression group. STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

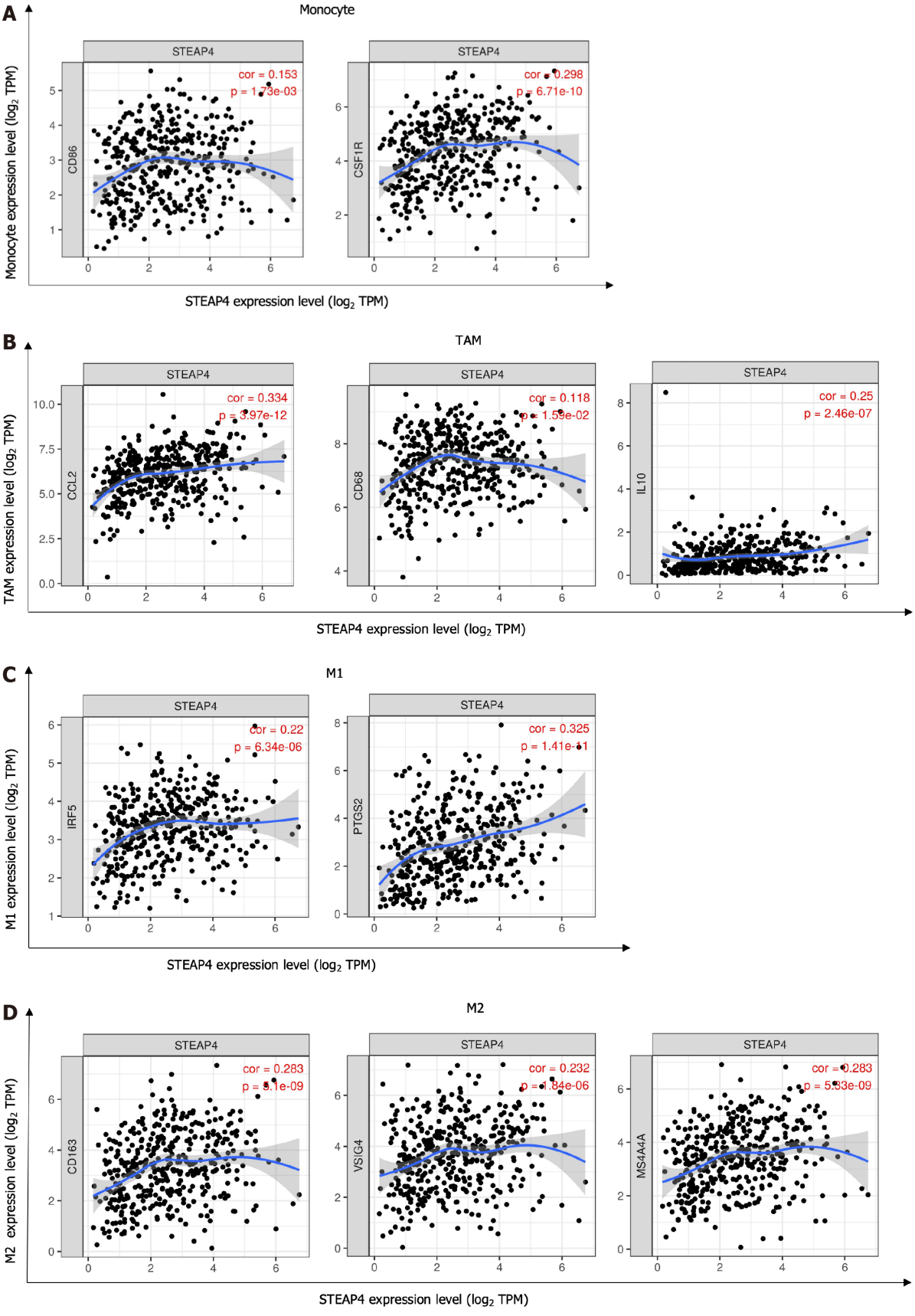


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Figure 5 Six-transmembrane epithelial antigen of the prostate 4 expression correlates with macrophage infiltration in stomach adenocarcinoma (*n* = 415). A-D: Scatter plots of associations between six-transmembrane epithelial antigen of the prostate 4 and gene markers, including CD86, CSF1R of monocytes (A); CCL2, CD68, and IL10 of TAMs (B); IRF5, PTGS2 of M1 macrophages (C); and CD163, VSIG4, and MS4A4A of M2 macrophages (D). STAD: Stomach adenocarcinoma; TAM: Tumor-associated macrophage; STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

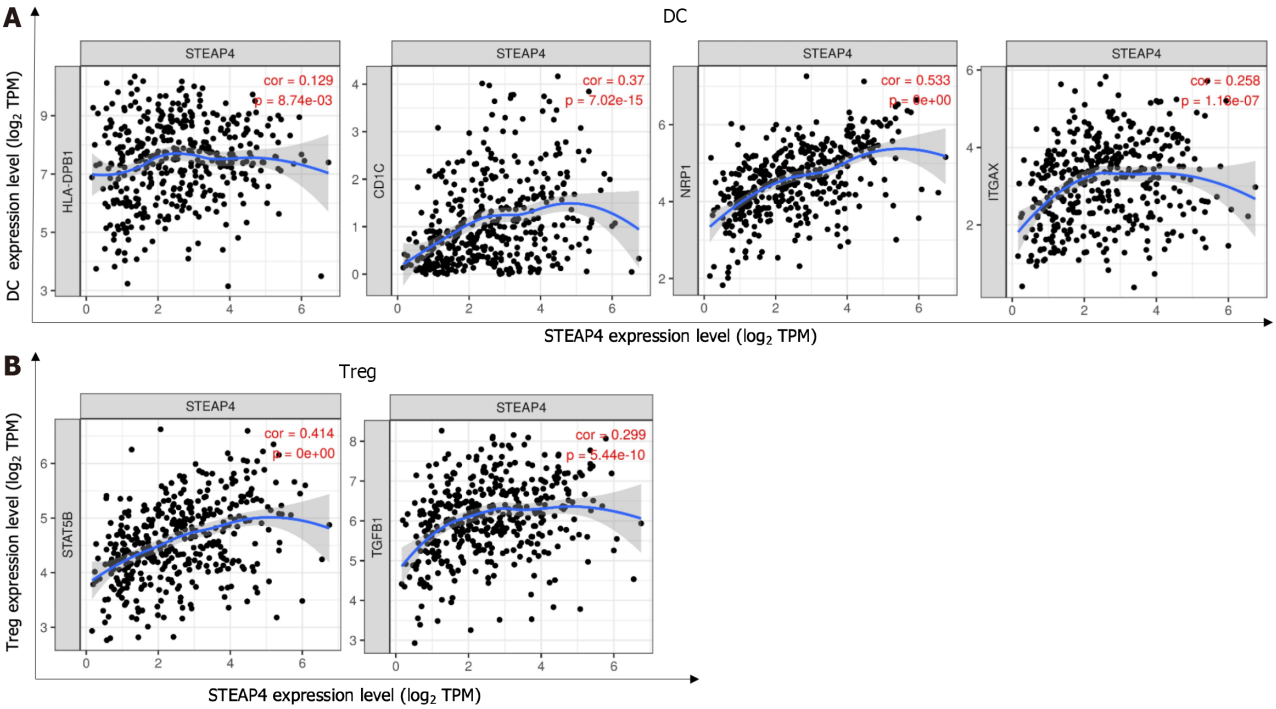

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Figure 6 The close relationship between six-transmembrane epithelial antigen of the prostate 4 and dendritic cell and Treg cell infiltration. Scatter plots of associations between six-transmembrane epithelial antigen of the prostate 4 and markers, including HLA-DPB1, CD1C, NRP1, and ITGAX of dendritic cells (A); and STAT5B, TGFB1 of Tregs (B). DC: Dendritic cell; Treg: Regulatory T cell; STEAP4: Six-transmembrane epithelial antigen of the prostate 4.

DCs promote tumor metastasis by increasing the activity of Treg cells and decreasing the activity of CD8+ T cells[25]. Here, high expression of STEAP4 was correlated with a high degree of DC infiltration, and DC markers such as HLA-DPB1, CD1C, NRP1 and ITGAX were also significantly correlated with STEAP4 expression ($P < 0.01$). In addition, STEAP4 was positively correlated with, that is STAT5B and TGFB1, biomarkers of Treg cells (Table 3, Figure 6), indicating a close relationship between STEAP4 and DC and Treg cell infiltration. However, whether STEAP4 can also mediate DC and tumor metastasis needs further research.

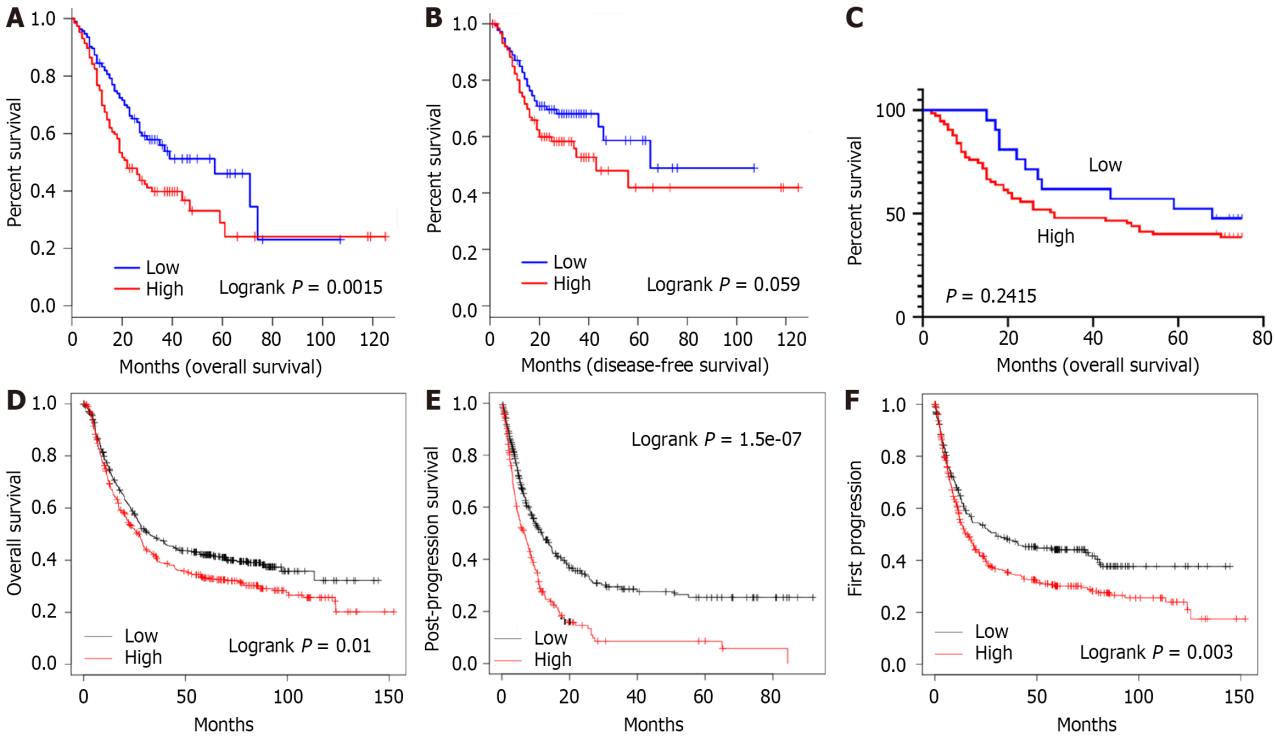
High expression of STEAP4 predicts poor prognosis in patients with GC

Based on the increased level of STEAP4 expression in GC, the prognostic value of STEAP4 was also evaluated on survival rate by using GEPIA database. It is worth noting that the expression of STEAP4 affects prognosis in all GC patients, and patients with high expression of STEAP4 have poor OS ($P = 0.0015$) and disease-free survival (DFS) ($P = 0.059$) (Figure 7A and B).

For immunohistochemical staining of STEAP4, it is showed that STEAP4 expression was not significantly correlated with OS. Although the difference did not meet statistical criteria ($P > 0.05$), high expression of STEAP4 tended to predict shorter OS in patients with GC, suggesting that STEAP4 protein levels could be used as a predictor of survival in patients with GC (Figure 7C). For further investigation, the Kaplan-Meier Plotter database was also applied to evaluate the prognostic signature of STEAP4. Interestingly, poor prognosis [OS: HR = 1.25, 95%CI: 1.05-1.48, $P = 0.01$; post-progression survival (PPS): HR = 1.8, 95%CI: 1.44-2.25, $P = 1.5e-07$; first progression (FP): HR = 1.38, 95%CI: 1.11-1.70, $P = 0.003$] was correlated with higher STEAP4 expression, suggesting that the level of STEAP4 influences the prognosis of GC patients (Figure 7D-F).

DISCUSSION

It is accepted that STEAP4 is an inflammatory metal reductase to catalyze the reduction of copper and iron, and the oxidation of NADPH. It has been shown that STEAP4 expression can promote the uptake of iron and copper, which can only be transported in reduced form through the cell membrane to exert their effects[9,14,26]. Liao *et al*[9] recently reported higher levels of cellular copper can enhance and maintain the activation of NF-κB, which leads to the production of inflammatory cytokines and chemokines, and Zhao *et al*[27] found STEAP4-mediated chemokine and cytokine induction enhances recruitment and activation of immune cells. As an important type of malignancy in gastrointestinal tract, GC is significantly associated with inflammatory and immune infiltration, both of which interact with the tumor microenvironment[28]. However, the regulatory factors in GC are not well characterized regarding inflammatory and immune infiltration.



DOI: 10.5306/wjco.v14.i8.297

Figure 7 High expression of six-transmembrane epithelial antigen of the prostate 4 tends to be associated with poor prognosis in the patients of gastric cancer. A and B: Survival curves of overall survival (OS) and disease-free survival in the Gene Expression Profiling Interactive Analysis database (n = 384); C: Survival curves of OS in the tissue chip (n = 96); D-F: Survival curves of OS (D), post-progression survival (E), and first progression (F) in the Kaplan-Meier Plotter database (n = 875, n = 498, and n = 640). OS: Overall survival; DFS: Disease-free survival; PPS: Post-progression survival; FP: First progression.

Here, current research focused on STEAP4, a reductase related to oxidation, and its role in the progression of GC. We found that changes in STEAP4 expression levels are associated with the prognosis of GC, predicting poor prognosis of GC patients. Interestingly, high STEAP4 expression had a tendency to promote lymph node metastasis and vascular invasion, proposing STEAP4 as a predictor of tumor metastasis. In addition, we also show that in GC, the level of immune infiltration and multiple immune marker sets are correlated with STEAP4 expression level, and STEAP4 expression is positively correlated with stromal cells and immune cells of the tumor microenvironment. Thus, studies demonstrating the potential role of STEAP4 in tumor immunology and its use as a cancer biomarker provide insight.

In current investigation, we used a GC tissue microarray to determine the expression level of STEAP4 in GC and its adjacent tissues, and prognosis. Based on the immunohistochemical analysis, STEAP4 is highly expressed in GC compared with normal tissues, and is associated with poor prognosis. Although there was a significant correlation between STEAP4 expression and clinicopathological parameters, patients with high STEAP4 expression tended to have a higher pathological stage, lymph node metastasis and vascular invasion. Analysis of the GC cohort in TCGA showed that increased expression of STEP4 is associated with higher clinical stage. Furthermore, analysis of data from GEPIA and Kaplan-Meier Plotter revealed that high levels of STEAP4 expression are associated with high hazard ratios of OS, DFS, PPS, and FP. Together, these findings suggest that STEAP4 may be a prognostic biomarker in GC.

Another important aspect of this study is that STEAP4 expression correlates with different levels of immune infiltration in GC. Our results show a moderate to strong positive correlation between the infiltration levels of M1/M2 macrophages and DCs with STEAP4 expression levels in GC, implicating a potential regulatory function of STEAP4 in tumor-associated macrophage infiltration. Moreover, there is a significant correlation between STEAP4 expression and the regulation of several markers of helper T cells (Trf, Th17, and Treg), and it is known that the recruitment of regulatory T cells (Tregs) is another mechanism of immunosuppression[29]. Tumor cells secrete chemokines to attract Tregs and promote tumor angiogenesis[30], indicating that STEAP4 is a potential source for regulating T cell function in GC.

In addition, ESTIMATE algorithm analysis showed that high STEAP4 expression is positively correlated with stromal cells and immune cells. Interestingly, cancer develops in a complex tissue environment, and they rely on this environment for continuous growth, invasion and metastasis. Studies have shown that under the influence of carcinogenic factors, various cells in the tumor microenvironment undergo metabolic changes, which creates favorable conditions for the occurrence and development of tumors[31]. Not only immune cells, but also other stromal cells constituting the TME are also involved through metabolic reprogramming. Metabolites of stromal cells and immune cells not only serve as nutrient reservoirs to provide energy sources for tumor growth, but also act as messengers to transmit intercellular signals and participate in a variety of tumor-promoting signaling pathways[32]. This may be due to the recruitment of tumor-mediated immune cells by various chemokines secreted by tumor cells through activation of relevant signals in the TME[33]. Therefore, these results reveal that STEAP4 is specifically associated with immune-infiltrating cells, suggesting

that STEAP4 plays a role in immune escape in the microenvironment of GC.

CONCLUSION

The present study found that STEAP4 is a cancer-promoting factor in GC and can be used as a prognostic indicator in GC patients. GC patients with high expression of STEAP4 have a shorter survival time, and may play an important role in immune cell infiltration in GC patients, as well as serve as a prognostic biomarker.

ARTICLE HIGHLIGHTS

Research background

Six-transmembrane epithelial antigen of the prostate 4 (STEAP4), a transmembrane protein involved in metal reductase transport of copper and iron, has been reported as a potential target for cellular and antibody immunotherapy.

Research motivation

Few studies on STEAP4 in gastric cancer (GC), which may play a role in the immune response to the occurrence and development of GC.

Research objectives

The expression of STEAP4 in GC tissues and its correlation with the level of tumor immune infiltration were comprehensively analyzed and to explore the potential immune effect of STEAP4 in GC.

Research methods

The protein expression level, clinicopathological parameters and prognosis of STEAP4 in tumor and adjacent tissues of GC patients were detected by immunohistochemistry. An online database was used to study the correlation between STEAP4 and the level of tumor immunoinfiltration and the characteristics of immunoinfiltration genes. The relationship between STEAP4 expression and immune and stromal scores in the GC was analyzed by ESTIMATE algorithm.

Research results

Immunohistochemistry analysis showed that STEAP4 was highly expressed in GC and was positively correlated with the clinical stage of GC. The infiltration levels of immune cells such as B cells, CD4+ T cells, macrophages, neutrophils and dendritic cells were positively correlated with STEAP4. The expression level of STEAP4 was strongly correlated with most of the immune markers. In addition, the ESTIMATED algorithm analysis showed that the stromal, immune and estimated scores were higher in the group with high expression of STEAP4, while the tumor purity was higher in the STEAP4 Low expression group. The relationship between STEAP4 expression and prognosis of GC patients was further studied, and the results showed that high STEAP4 expression had shorter overall survival and disease-free survival. Moreover, Kaplan-Meier Plotter showed that high expression of STEAP4 was associated with poor survival in patients with GC.

Research conclusions

STEAP4 is indicated as a potential immune indicator of GC, targeting STEAP4 may provide a new therapeutic method for GC patients.

Research perspectives

The comprehensive analysis of STEAP4 function in GC still needs to explore the mechanism by which STEAP4 plays an immune role in GC.

FOOTNOTES

Author contributions: Liu J and Fang ZX designed the research study; Fang ZX performed the research; Fang ZX, Hou YY, Wu Z, Wu BX, Deng Y, and Wu HT analyzed the research and wrote the manuscript; Liu J revised the manuscript critically; and all authors have read and approved the final manuscript.

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Institutional review board statement: The current study was reviewed and approved by the Ethics Committee of Shantou University Medical College (Approval No. SUMC-2022-075).

Informed consent statement: The informed consent was waived by the Ethics Committee because our experiment was conducted on commercial microarray.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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ORIGINAL ARTICLE

Retrospective Study

Readmission rates and outcomes in adults with and without COVID-19 following inpatient chemotherapy admission: A nationwide analysis

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has received considerable attention in the scientific community due to its impact on healthcare systems and various diseases. However, little focus has been given to its effect on cancer treatment.

AIM

To determine the effect of COVID-19 pandemic on cancer patients' care.

METHODS

A retrospective review of a Nationwide Readmission Database (NRD) was conducted to analyze hospitalization patterns of patients receiving inpatient

chemotherapy (IPCT) during the COVID-19 pandemic in 2020. Two cohorts were defined based on readmission within 30 d and 90 d. Demographic information, readmission rates, hospital-specific variables, length of hospital stay (LOS), and treatment costs were analyzed. Comorbidities were assessed using the Elixhauser comorbidity index. Multivariate Cox regression analysis was performed to identify independent predictors of readmission. Statistical analysis was conducted using Stata® Version 16 software. As the NRD data is anonymous and cannot be used to identify patients, institutional review board approval was not required for this study.

RESULTS

A total of 87755 hospitalizations for IPCT were identified during the pandemic. Among the 30-day index admission cohort, 55005 patients were included, with 32903 readmissions observed, resulting in a readmission rate of 59.8%. For the 90-day index admission cohort, 33142 patients were included, with 24503 readmissions observed, leading to a readmission rate of 73.93%. The most common causes of readmission included encounters with chemotherapy (66.7%), neutropenia (4.36%), and sepsis (3.3%). Comorbidities were significantly higher among readmitted hospitalizations compared to index hospitalizations in both readmission cohorts. The total cost of readmission for both cohorts amounted to 1193000000.00 dollars. Major predictors of 30-day readmission included peripheral vascular disorders [Hazard ratio (HR) = 1.09, $P < 0.05$], paralysis (HR = 1.26, $P < 0.001$), and human immunodeficiency virus/acquired immuno-deficiency syndrome (HR = 1.14, $P = 0.03$). Predictors of 90-day readmission included lymphoma (HR = 1.14, $P < 0.01$), paralysis (HR = 1.21, $P = 0.02$), and peripheral vascular disorders (HR = 1.15, $P < 0.01$).

CONCLUSION

The COVID-19 pandemic has significantly impacted the management of patients undergoing IPCT. These findings highlight the urgent need for a more strategic approach to the care of patients receiving IPCT during pandemics.

Key Words: Chemotherapy; Coronavirus disease 2019 pandemic; Nationwide readmission database; Readmission rates; Cancer; Healthcare cost

Core Tip: Our nationwide study explored care for patients undergoing inpatient chemotherapy during the coronavirus disease 2019 (COVID-19) pandemic. It is the first to analyze factors surrounding hospitalization for such patients. We found a higher readmission rate during the pandemic, with comorbidities posing a greater risk. Surprisingly, COVID-19 infection was not significantly linked to readmission. Hospitalization costs rose, averaging 22952.00 dollars. Our findings would interest the scientific community, hospital managers, and health policymakers. Understanding the pandemic's impact on cancer patients' care can lead to mitigating health policies.

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INTRODUCTION

On the 11th of March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic following its discovery in December 2019 in Wuhan, China[1,2]. Since then, WHO has reported over 756 million cases and 6.8 million deaths worldwide[3], with the United States alone accounting for over 100 million cases and 1 million deaths[3]. COVID-19 is caused by a virus known as severe acute respiratory syndrome coronavirus 2[4], which results in a range of respiratory symptoms from mild to severe[4]. However, the introduction and widespread administration of COVID-19 vaccines have contributed to a decline in infection rates[5].

The COVID-19 pandemic has had a profound impact on various aspects of human life[6], with healthcare services and delivery being particularly affected[7,8]. The 30-day readmission rate serves as a crucial metric used by the Center for Medicare and Medicaid Services to evaluate hospitals and assess the quality of healthcare services[9,10]. In 2012, the Center for Medicare and Medicaid Services introduced the Hospital Readmission Reduction Program to enhance healthcare quality and reduce costs[11]. The annual cost associated with readmissions averages between 15 and 20 billion dollars[12]. Reducing the 30-day readmission rates can significantly decrease healthcare costs and alleviate the strain on healthcare facilities[13]. Assessing readmission rates becomes even more important for patients undergoing chemotherapy, as chemotherapy often entails extended periods of treatment and substantial healthcare expenses[13]. A systematic review conducted prior to the COVID-19 pandemic revealed readmission rates ranging from 3% to 34% for

patients undergoing chemotherapy[14]. Another study by Tennison *et al*[14] reported a 55% readmission rate for patients undergoing chemotherapy in United States hospitals. However, since the onset of the COVID-19 pandemic, there has been a scarcity of data regarding the hospitalization and care of patients receiving chemotherapy during this period.

This study aims to investigate the impact of the COVID-19 pandemic on 30-day and 90-day readmission rates among patients hospitalized for inpatient chemotherapy (IPCT). We also aim to identify common causes and independent predictors of readmission in this patient population. By conducting this study, we aim to gain a deeper understanding of the effects of COVID-19 on the management of cancer patients. Furthermore, the findings of this study can contribute to the development of strategies that improve the care of cancer patients. Finally, we believe that this study will pave the way for further research on the effects of pandemics on healthcare infrastructure and services.

MATERIALS AND METHODS

Study design and data source

We conducted a retrospective cross-sectional review of hospitalizations for IPCT across the United States during a one-year period in 2020. Hospitalization data for 2020 was retrieved from the Nationwide Readmission Database (NRD). The NRD is a national database that captures patients' hospitalization, readmissions, and other relevant discharge histories from over 31 different states in the United States. The NRD is a product of the Healthcare Cost and Utilization Project (HCUP), State Inpatient Databases, and the Agency for Healthcare Research and Quality[9]. The database records over 40 International Classification of Diseases-10 (ICD-10) recognized diagnoses and 25 procedures[9]. It covers approximately 62.2% of the United States population and 60.8% of total hospitalizations in the country[15]. It contains unique, verified de-identified patient linkage that enables tracking of individual hospitalizations and readmissions. Data within the NRD is available from January 1 to December 31 each year, and information outside of these dates cannot be accessed[16]. With over 18 million hospital stays recorded, the NRD provides ample and suitable data for our study.

Data Collection

We collected data on adult hospitalizations (age >18 years) for IPCT during the COVID-19 pandemic in 2020. Hospitalizations for conditions other than IPCT and those involving patients under 18 years of age were excluded from the study. Additionally, hospitalizations in December were excluded due to the lack of an adjoining 30-day period to determine 30-day readmission. The hospitalizations were divided into two groups: The 30-day readmission cohort (30DRC) and the 90-day readmission cohort (90DRC). Within each cohort, we identified and tagged each case that met our inclusion criteria as an index case on the first admission. Each index case was traced for readmission within 30 d of admission and tagged as a 30-day readmission in the 30DRC. Similarly, each index case was traced for readmission within 90 d of admission and tagged as a 90-day readmission in the 90DRC. Specific patient data, including demographics (age, sex, health insurance type, household income), mortality on readmission, LOS, and cost of admission, were collected. Hospital-specific variables, such as type of hospital, bed size, and hospital location, were also obtained. To account for the effects of comorbid conditions, we utilized the Elixhauser Comorbidity Index (ECI) to assess the level of comorbidities in the hospitalizations. The ECI is a software tool developed as part of HCUP, which identifies 38 different pre-existing comorbidities in hospital administrative data[15]. The ECI software has been refined for ICD-10 comorbidities and is available in nationwide HCUP databases for years 2019 onwards[15]. The ECI demonstrates a better prognostic value compared to the Charlson comorbidity index[16].

Outcome measures

The primary outcome of our study was the all-cause 30-day and 90-day readmission rates. Secondary outcomes included demographic characteristics, insurance type, mortality rate during readmission, average LOS, average cost of readmission, and independent predictors of readmission.

Analysis method

All analyses were performed using weighted samples for national estimates in accordance with HCUP regulations for using the NRD[17]. Data analysis was conducted using Stata® Version 16 software (StataCorp, Texas, United States). We examined demographic characteristics and calculated mean age, sex distribution, and mean household income. Additionally, we analyzed hospital-specific features, including hospital location, teaching status, and bed size. Comorbidities were calculated as proportions in our cohorts using the 31 ECI comorbidities, and the chi-square test was employed to compare characteristics between index hospitalizations and readmissions in 2020. A multivariate Cox regression analysis was performed to identify independent variables associated with readmission.

Ethical Consideration

As with other HCUP databases, the NRD data is anonymous and cannot be used to identify individual patients. Therefore, institutional review board approval was not required for our study.

RESULTS

We identified a total of 87756 hospitalizations for IPCT in the 2020 NRD database. In the 30DRC, we identified 55005 index hospitalizations during the study period. Among these, there were 32904 readmissions within 30 d, resulting in a 30-day readmission rate of 59.8%. Table 1 provides a comparison of the demographics of hospitalized patients between index hospitalizations and readmission cohort. Among the 90DRC, we identified 33636 index hospitalizations, of which 24503 patients were readmitted within 90 d of admission. The 90-day readmission rate was 73.93%. In both readmission cohorts, the proportion of male patients was higher than female patients. The majority of hospitalized patients in both cohorts were in their middle age. Private health insurance was the primary payer for hospital bills in most cases. A significant number of patients in both readmission cohorts belonged to the 26th-50th quantile of the national median household income. The rates of 30-day and 90-day readmission were higher in patients with Medicaid and private insurance, as well as those with a higher comorbidity burden (ECI score ≥ 4).

Comorbidities analyzed were significantly more prevalent in readmissions compared to index hospitalizations in both readmission cohorts. Detailed comparisons of comorbidities between index hospitalizations and readmissions in the 30DRCs and 90DRCs are listed in Tables 2 and 3, respectively. The majority of patients tested negative for COVID-19 in both index hospitalizations and readmissions, as depicted in Figure 1. Metropolitan teaching hospitals had the highest number of admissions in both cohorts. Table 4 summarizes the hospital characteristics among index hospitalizations and readmissions.

Common causes of readmission in both readmission cohorts included admissions for chemotherapy, neutropenia, non-specified sepsis, antineoplastic-induced pancytopenia, agranulocytosis secondary to chemotherapy, sepsis due to *Escherichia coli*, admissions for immunotherapy, acute myeloblastic leukemia, specified sepsis, and acute kidney failure. Figure 2 demonstrates the top causes of 30-day readmission during the COVID-19 pandemic. Mortality was higher among readmitted patients in both readmission cohorts. Figure 3 compares the mortality in index hospitalizations and 30DRCs and 90DRCs, respectively.

In both cohorts, readmissions had a shorter average LOS compared to index hospitalizations. The average LOS for readmitted patients was 5.60 d in the 30DRC, compared to 6.77 d for index cases ($P < 0.001$). In the 90DRC, the mean LOS for readmitted patients was 6.37 d, while index hospitalizations had a mean LOS of 7.51 d ($P < 0.001$). The total number of days lost due to hospitalization was higher in the 30DRC, totaling 184277 d compared to 156086 d in the 90-day cohort. The mean adjusted cost of hospitalization was higher in the 90-day cohort, with an average of 25646.4 dollars spent per index admission and 23477.0 dollars spent per readmission. In the 30DRC, the average cost per index admission was 22951.9 dollars, and 19220.8 dollars per readmission. The total cost incurred due to readmission across the country was 625 million dollars for the 30DRC and 568 million dollars for the 90DRC.

The results of the multivariable Cox regression analysis to identify independent predictors of 30-day and 90-day readmission are shown in Tables 5 and 6, respectively. Presence of comorbidities, including peripheral vascular disorder [Hazard ratio (HR) = 1.09, $P = 0.048$], paralysis (HR = 1.26, $P < 0.001$), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (HR = 1.14, $P = 0.03$), and lymphoma (HR = 1.23, $P < 0.001$), were associated with an increased risk of readmission for IPCT within 30 d of discharge during the COVID-19 pandemic. Being in the middle age group (HR = 0.83, $P < 0.001$), elderly age groups (HR = 0.78, $P < 0.001$), discharge against medical advice (HR = 0.69, $P = 0.031$), renal failure (HR = 0.89, $P = 0.004$), liver disease (HR = 0.9, $P = 0.02$), and coagulopathy (HR = 0.91, $P = 0.002$) were associated with a decreased risk of readmission within 30 d of discharge. Figure 4 shows a Kaplan-Meier readmission curve for 30-day readmissions by COVID-19 status, with a P-value < 0.01.

A similar profile of comorbidities increased the risk of 90-day readmission as observed in the 30DRC, except for HIV/AIDS (HR = 1.1, $P = 0.211$). Other variables analyzed for the risk of 90-day readmission followed the same trend as the 30DRC, except for coagulopathy (HR = 0.95, $P = 0.093$).

DISCUSSION

Our study provides a comprehensive nationwide view of the care received by patients undergoing IPCT during the COVID-19 pandemic. To the best of our knowledge, this is the first study that specifically focused on and analyzed factors related to hospitalization for patients receiving IPCT during the pandemic. We observed a 30-day readmission rate of 58.9% and a 90-day readmission rate of 73.93%, both of which are significantly higher than rates reported in previous similar studies[18,19]. This increase can be attributed to the strain imposed on the healthcare system by the pandemic. Similar findings were reported by Loo *et al*[20] and Matthews *et al*[21], who also observed an increase in readmission rates during the COVID-19 pandemic. The demographics of our patients were comparable and consistent with those reported in studies conducted before the pandemic[11,22].

Several studies conducted during the pandemic have reported higher costs of hospitalization, and our study aligns with these findings[23,24]. With an average cost of re-hospitalization of 22952.0 dollars observed in our study, the cost was significantly higher than the average cost of 17035 dollars reported in similar hospitalizations before the pandemic [25]. However, contrary to the findings of higher readmission costs compared to index admissions reported by Kwei-Nsoro *et al*[9], our study revealed a higher cost of index admission.

The ECI scores were higher among readmitted hospitalizations compared to index hospitalizations due to the higher comorbidity burden among readmitted patients. Higher ECI scores are associated with higher mortality[26,27], which was also observed in our study, consistent with previous studies[28,29].

Table 1 Comparison of patients' demographics between inpatient chemotherapy and readmission for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables (unit)	Index admission	30 d readmission	*P* value
Mean age ± SD (yr)	54.7 ± 17.71	53.53 ± 17.94	
Age range categories (%)			< 0.001
18-44 yr	26.86	29.5	
45-64 yr	40.06	39.62	
65 yr and above	33.08	30.89	
Sex (%)			0.182
Male	58.07	58.47	
Female	41.93	41.53	
Payer type (%)			< 0.001
Medicare	34.43	32.33	
Medicaid	17.06	18.14	
Private insurance	46.14	47.25	
Self pay	2.36	2.28	
Median household income (%)			0.617
0-25th quintile	22.28	21.96	
26th-50th quintile	27.91	28.02	
50th-75th quintile	25.61	25.85	
> 75th quintile	24.19	24.18	
ECI score (%)			< 0.001
0	4.88	4.14	
1	18.61	17.7	
2	23.75	23.35	
3	20.61	20.53	
≥ 4	32.15	34.28	

ECI: Elixhauser comorbidity index.

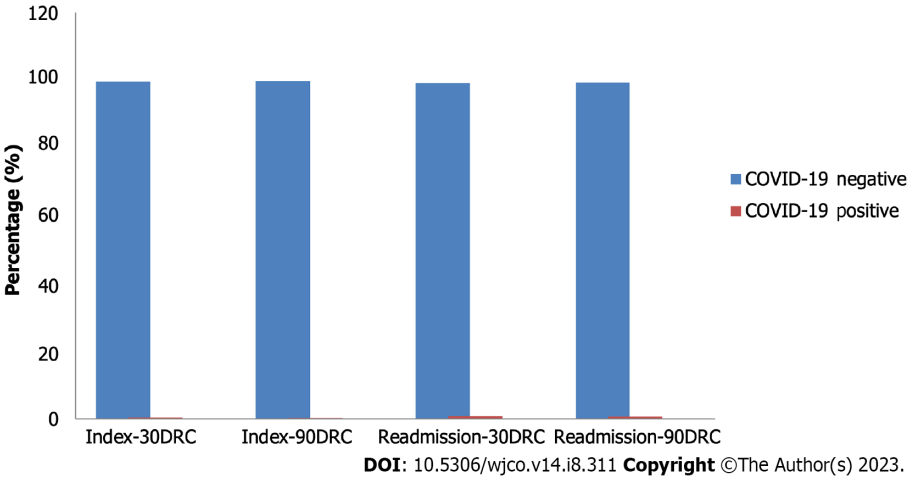

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Figure 1 Coronavirus disease 2019 status of index and readmitted case for 30-days and 90-days readmission cohort, 2020. COVID-19: Coronavirus disease 2019; DRC: Day readmission cohort.

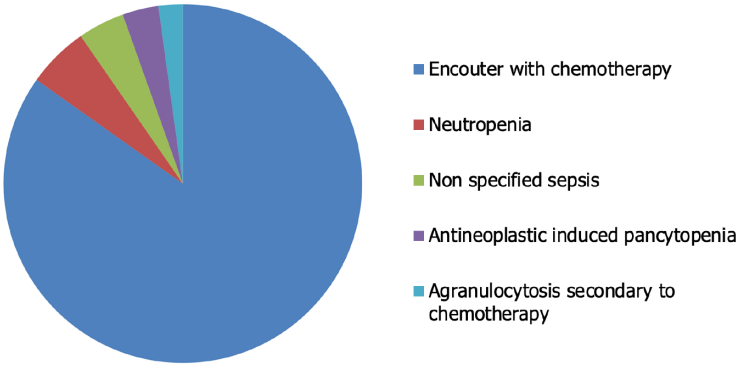

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Figure 2 Top five causes of 30-days readmission for inpatient chemotherapy during coronavirus disease 2019 pandemic, Nationwide Readmission Database, 2020.

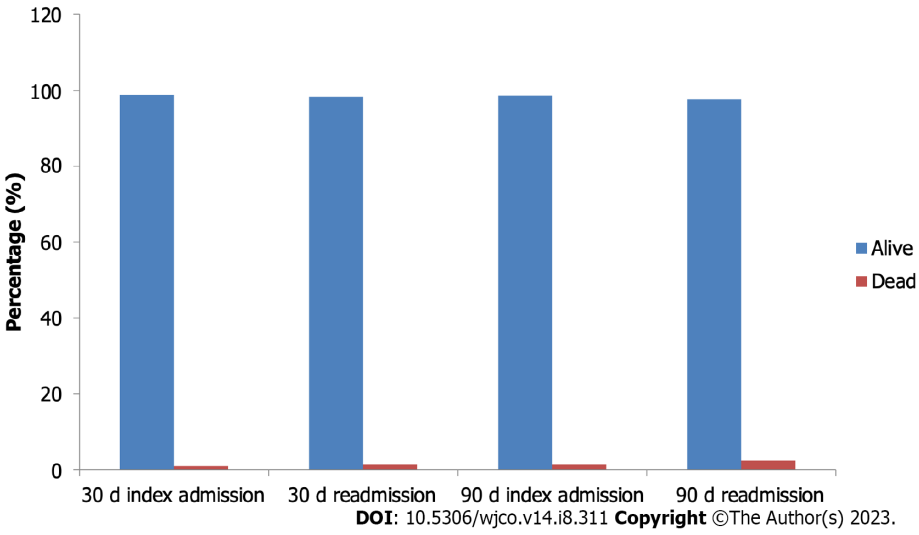

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Figure 3 Comparison of Mortality Between Index Admission and Readmission in 30-days and 90-days readmission cohort, Nationwide Readmission Database, 2020.

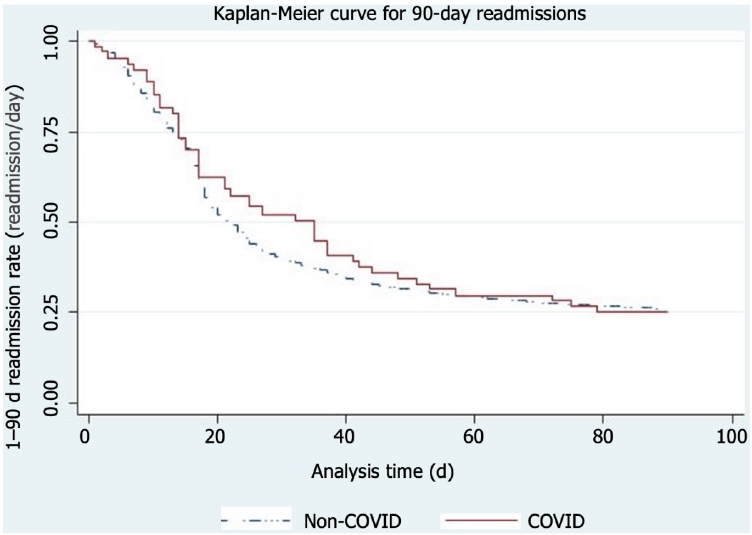

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Figure 4 Kaplan-Meier curve for 90-readmision, Nationwide Readmission Database, 2023. COVID: Coronavirus disease.

Table 2 Comparing the 31 elixhauser comorbidities between index admission and 30-days readmission for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables (%)	Index	Readmission	*P* value
Congestive heart failure	5.45	5.83	0.02
Cardiac arrhythmias	12.14	13.13	< 0.001
Valvular diseases	2.48	2.12	0.001
Pulmonary circulation disorders	2.1	2.47	0.001
Peripheral vascular disorders	4.81	5.1	0.141
Hypertension, uncomplicated	34.12	32.88	0.001
Paralysis	1.06	1.17	0.181
Other neurologic disorders	4.72	5.72	< 0.001
Chronic pulmonary disease	11.07	10.5	0.012
Diabetics, uncomplicated	8.44	8.5	0.757
Diabetics, complicated	8.63	8.28	0.105
Hypothyroidism	9.88	9.61	0.134
Renal failure	7.75	6.89	< 0.001
Liver disease	4.06	4.09	0.854
Peptic ulcer disease	0.34	0.33	0.859
HIV/AIDS	1.26	1.44	0.003
Lymphoma	45.89	48.77	< 0.001
Metastatic cancer	14.93	14.78	0.637
Solid tumor without metastasis	24.4	24.84	0.255
RA/collagen vascular disease	2.03	1.9	0.226
Coagulopathy	12.64	14.41	< 0.001
Obesity	10.33	9.81	0.159
Weight loss	10.76	11.12	0.207
Fluid and electrolyte disorders	23.17	28.16	< 0.001
Blood loss anemia	0.39	0.35	0.497
Deficiency anemia	3.09	2.63	0.001
Alcohol abuse	1.13	0.98	0.103
Drug abuse	2.32	2.35	0.832
Psychosis	0.68	0.76	0.089
Depression	12.39	12.59	0.429
Hypertension, complicated	8.04	7.66	0.063

HIV/AIDS: Human immunodeficiency virus/acquired immuno-deficiency syndrome; RA: Rheumatoid arthritis.

The most common cause of readmission was admission for chemotherapy. The Kaplan-Meier curve (Figure 4) demonstrated a shorter time to 50% readmission in the non-COVID-19 group (20 d) compared to the COVID-19 group (36 d). This could be explained by the fact that COVID-19 positivity delayed the admission for chemotherapy, which was the most common cause of readmissions. Other causes of readmissions included neutropenia, sepsis, and acute kidney injury, in line with previous studies[13,30].

We observed a significant number of patients undergoing IPCT being managed in medium-sized metropolitan teaching hospitals. However, we did not observe any significant difference in the type of treatment center between index hospitalizations and readmissions. Middle-aged and elderly patients had a decreased risk of readmission, likely due to the higher prevalence of comorbidities in these age groups. Our results showed that comorbidities were associated with an increased risk of readmission, consistent with findings in other studies[31,32].

Table 3 Comparison of the 31 elixhauser comorbidities between index admission and 90-days readmission for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables (%)	Index	Readmission	*P* value
Congestive heart failure	5.88	6.59	0.002
Cardiac arrhythmias	13.16	14.17	0.001
Valvular diseases	2.69	2.19	0.001
Pulmonary circulation disorders	2.28	2.57	0.052
Peripheral vascular disorders	4.72	5.19	0.024
Hypertension, uncomplicated	34.58	33.12	< 0.001
Paralysis	1.09	1.13	0.645
Other neurologic disorders	4.81	5.91	< 0.001
Chronic pulmonary disease	11.68	11.09	0.026
Diabetics, uncomplicated	8.54	8.51	0.908
Diabetics, complicated	8.86	8.7	0.539
Hypothyroidism	10.31	9.77	0.003
Renal failure	8.38	7.88	0.033
Liver disease	4.36	4.42	0.814
Peptic ulcer disease	0.29	0.37	0.196
HIV/AIDS	1.09	1.12	0.667
Lymphoma	43.95	44.89	0.012
Metastatic cancer	15.5	14.48	< 0.001
Solid tumor without metastasis	24.39	23.94	0.181
RA/collagen vascular disease	2.13	1.91	0.077
Coagulopathy	13.27	15.73	< 0.001
Obesity	10.41	9.77	0.166
Weight loss	11.8	12.44	0.055
Fluid and electrolyte disorders	24.87	30.26	< 0.001
Blood loss anemia	0.44	0.42	0.876
Deficiency anemia	3.16	2.51	< 0.001
Alcohol abuse	1.29	1.13	0.144
Drug abuse	2.33	2.31	0.922
Psychosis	0.71	0.77	0.269
Depression	12.23	12.95	0.015
Hypertension, complicated	8.81	8.75	0.785

HIV/AIDS: Human immunodeficiency virus/acquired immuno-deficiency syndrome; RA: Rheumatoid arthritis.

Previous studies have indicated that discharge against medical advice increases the risk of readmission, but our results were contrary to this[16,32]. This could be explained by the possibility that patients who left the hospital against medical advice had limited access to the healthcare system, which was heavily impacted by the pandemic[8,33]. However, further research is needed to explore this area. We found weight loss to be an independent predictor of 90-day readmission, which is consistent with a survey of approximately 10000 general medicine discharges where weight loss was identified as a significant predictor of 30-day readmissions, aligning with our findings in the 90DRC[33]. However, we did not find weight loss to be an independent predictor of 30-day readmission, and the reason for this remains unclear. Additionally, contrary to our expectations and findings in similar studies[21,34], COVID-19 was not identified as an independent predictor of readmission. This could be due to the smaller percentage of COVID-19-infected patients in our study population or could be an area for further investigation.

Table 4 Comparison of hospital specific characteristics of index admissions and readmissions for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables	Index	Readmission	*P* value
Hospital bed size (%)			0.002
Small	7.51	8.49	
Medium	15.96	16.01	
Large	76.53	75.5	
Teaching status of hospital (%)			0.002
Metropolitan, non teaching	5.51	6.09	
Metropolitan teaching	93.48	92.27	
Non-metropolitan	1.01	1.64	

Finally, we acknowledge some limitations in our study. The readmission rates may vary across different states, but the NRD does not provide state-specific data, preventing us from drawing conclusions at the state level. Our study excluded elective hospitalizations in December, potentially leading to a missed number of readmissions during that month.

CONCLUSION

The COVID-19 pandemic has significantly impacted the management of patients receiving IPCT. There is a need for a more strategic approach in the care of patients undergoing IPCT during pandemics.

Table 5 Independent predictors of 30 d readmission for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables	Hazard ratio	Confidence interval	*P* value
Age category			
45-64 years	0.83	0.79-0.87	< 0.001
65 years and above	0.78	0.72-0.85	< 0.001
Discharge AMA	0.69	0.49-0.97	0.031
Payer type			
Medicaid	1.04	0.97-1.12	0.299
Private insurance	1.02	0.99-1.09	0.564
Self pay	1.05	0.90-1.23	0.522
Median household income			
25^{th}-50^{th} quantile	1.04	0.97-1.12	0.137
50^{th}-75^{th} quantile	1.04	0.96-1.09	0.103
> 75^{th} quantile	1.03	0.90-1.09	0.263
COVID-19	0.91	0.68-1.22	0.543
Comorbidities			
Congestive heart failure	0.92	0.85-1.00	0.059
Cardiac arrhythmias	0.96	0.91-1.01	0.147
Peripheral vascular disorders	1.09	1.00-1.19	0.048
Hypertension, uncomplicated	1.03	0.99-1.07	0.111
Paralysis	1.26	1.08-1.47	0.003
Chronic pulmonary disease	0.96	0.91-1.02	0.233
Diabetics, uncomplicated	0.94	0.89-1.00	0.058

Renal failure	0.89	0.82-0.96	0.004
Liver disease	0.9	0.82-0.98	0.023
HIV/AIDS	1.14	1.01-1.30	0.038
Lymphoma	1.23	1.17-1.28	< 0.001
Coagulopathy	0.91	0.86-0.97	0.002
Weight loss	0.97	0.92-1.04	0.457
Hypertension, complicated	1.05	0.96-1.15	0.28

AMA: Against medical advice; HIV/AIDS: Human immunodeficiency virus/acquired immuno-deficiency syndrome.

Table 6 Independent predictors of 90 d readmission for inpatient chemotherapy, Nationwide Readmission Database, 2020

Variables	Hazard ratio	Confidence interval	*P* value
Age category			
45-64 yr	0.84	0.80-0.89	< 0.001
65 yr and above	0.74	0.68-0.80	< 0.001
Discharge AMA	0.65	0.47-0.90	0.01
Payer type			
Medicaid	1.02	0.95-1.09	0.633
Private insurance	1.02	0.95-1.08	0.631
Self pay	1.15	0.99-1.33	0.056
Median household income			
25^{th}-50^{th} quintile	1.03	0.97-1.09	0.329
50^{th}-75^{th} quintile	1.04	0.98-1.11	0.166
> 75^{th} quintile	1.03	0.96-1.10	0.471
COVID-19	0.88	0.66-1.18	0.396
Comorbidities			
Congestive heart failure	0.93	0.85-1.01	0.086
Cardiac arrhythmias	0.97	0.92-1.02	0.198
Peripheral vascular disorders	1.15	1.04-1.26	0.004
Hypertension, uncomplicated	1.02	0.98-1.07	0.296
Paralysis	1.21	1.02-1.43	0.027
Chronic pulmonary disease	0.97	0.92-1.03	0.386
Diabetics, uncomplicated	0.92	0.87-0.99	0.01
Renal failure	0.91	0.83-0.99	0.046
Liver disease	0.89	0.82-0.98	0.017
HIV/AIDS	1.1	0.94-1.29	0.211
Lymphoma	1.14	1.09-1.20	< 0.001
Coagulopathy	0.95	0.90-1.00	0.093
Weight loss	0.93	0.88-0.99	0.019
Hypertension, complicated	1.03	0.93-1.14	0.604

AMA: Against medical advice; HIV/AIDS: Human immunodeficiency virus/acquired immuno-deficiency syndrome.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on healthcare services and has resulted in modifications to the management of various diseases.

Research motivation

The treatment of cancer has undergone significant changes during the COVID-19 pandemic. Understanding the effects of these changes can provide valuable insights to better prepare for future pandemics.

Research objectives

This study aims to provide insights into the outcomes of hospitalization for in hospital chemotherapy during the COVID-19 pandemic.

Research methods

We conducted a retrospective review of a Nationwide Readmission Database for patients undergoing inpatient chemotherapy (IPCT) during the COVID-19 pandemic. We analyzed data on readmission rates, causes of readmission, and predictors of readmission.

Research results

We found a 90-day readmission rate of 59.8% and a 30-day readmission rate of 73.93%. The most common cause of readmission was chemotherapy encounters (66.7%). Predictors of readmission included peripheral vascular disorders [Hazard ratio (HR) = 1.09, P = 0.04] and paralysis (HR = 1.26, P < 0.001). The total cost incurred due to readmission during the pandemic was 1193000000.00 dollars.

Research conclusions

The COVID-19 pandemic has had a significant impact on the management of cancer patients. There is a need for a more strategic approach to the care of patients undergoing IPCT during pandemics.

Research perspectives

This study opens the door for further investigation into the effects of pandemics on disease management.

FOOTNOTES

Author contributions: Kanemo P and Shaka H conceived of the presented idea and designed and proposed the study protocol; Deenadayalan V and Litvin R extracted data from the nationwide readmission database; Shaka A and Baskaran N provided tools for analysis and conducted the analysis; Musa KM, Shaka H and Odeyemi OE interpreted the analysis results and wrote the manuscript; Shaka H and Kanemo P supervised the findings of this work; all authors discussed the results and contributed to the final manuscript.

Institutional review board statement: As the nationwide readmission database data is anonymous and cannot be used to identify patients, institutional review board approval was not required for this study.

Informed consent statement: As the nationwide readmission database data is anonymous and cannot be used to identify patients, informed consent statement was not required for this study.

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