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REVIEW

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Men's gallbladder cancer: epidemiology, prevention, and treatment strategies

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Abstract

Herein, it was aimed to review the epidemiology, prevention, and treatment strategies for men's gallbladder cancer (GBC). "Gallbladder cancer" and "GBC" were searched in four online databases (PubMed, ScienceDirect, Scopus and Google Scholar). Six from 987 articles were selected after inclusion and exclusion processes. Data were collected online from all the studies. It was confirmed that GBC began with the weight control through glucagon-like peptide 1 (GLP-1), type 2 diabetes treatment, or healthy diet. GBC treatment strategies included surgery, chemotherapy and targeted therapies. New oral agents such as varlitinib, capecitabine, trifluridine/tripiracil (FTD/TPI), and pemigatinib with olaparib were employed as the second-line treatment for GBC. Understanding the epidemiology, prevention, and treatment strategies regarding GBC could minimize its negative prognosis and provide support for developing new therapies in future. Despite the continuous advancements pertaining to cancers, studies had been lacking on GBC. More information on GBC regarding prevention and treatment strategies would improve its handling.

Keywords

Gallbladder cancer; Epidemiology; Prevention; Treatment strategies

1. Introduction

Gallbladder cancer (GBC) is a rare aggressive malignancy with difficulties in earlier detection and poor prognosis even when diagnosed in time. GBC is treated *via* surgery and chemotherapy, however, resistance develops against chemotherapy [1]. GBC recurrence rate is 60–70%, while the 5-year survival is 5–15% [2]. GBC is the 6th most prevalent gastrointestinal cancer globally. Its pathogenesis remains unknown, however, it is perceived to be caused by chronic inflammation, dysplasia or carcinoma-*in-situ* which may progress to invasive cancer [3].

An assessment of the global mortality risk from digestive cancers (stomach, liver, esophagus, pancreas and GBC) as of 2020 is attributed to smoking, alcohol consumption and lifestyle [4]. The gallstones prevalence leads to GBC. GBC has poor prognosis, and its diagnosis can be delayed by vague symptoms. GBC is relatively rare, however the biliary tract cancer is common and its earlier diagnosis is critical to avoid fatality [5]. These gallbladder diseases have high incidence because of the environmental factors [6]. Sedentary lifestyle, obesity or rapid weight loss are particularly the common causes. Women are more prone to GBC. In addition, formation of cholesterol gallstone, cholelithiasis, advanced age, chronic inflammation affecting the gallbladder, biliary tract abnormalities, and gallbladder polyps are the other risk factors [7]. There is thus a need of studies on diagnosis, prevention, and treatment to predict the overall survival of GBC *via* nomograms, and by employing the independent predictors of T stage, N metastasis, peritoneal metastasis, resection and histology. Furthermore, discriminatory and corrective power need to be demonstrated [8]. The diagnosis and identification of GBC can also be based on pain, swelling, tumors or lumps being felt during abdominal pain or pain in the upper right of stomach. Abdominal bloating, fever, sudden weight loss, nausea, skin yellowing or whitish eyes are the early signs of GBC [9]. No standard GBC treatment is available, however chemotherapy is important in GBC including biliary capecitabine (BILCAP), gemcitabine plus radiotherapy, and cisplatin-gemstabine chemotherapy [10]. GBC is closely linked with mortality, particularly in the presence of liver metastases where tumor grade has been identified as a risk factor [11]. GBCs treatment requires more comprehensive approach compared to other diseases. Surgical excision has been the key, however there is a shift toward prevention as the conducive method of treatment [12]. Therefore, studies on GBC are important pertaining to chemotherapy, targeted therapy and immunotherapy in treating tumor cells which may also improve the patients prognosis [13, 14]. Overall, studies lack regarding GBC compared to other malignancies, however number of studies are being currently conducted [15].

This study analyzed major online databases, *i.e.*, PubMed, ScienceDirect, Scopus and Google Scholar to search for the clinically relevant studies on GBC epidemiology, prevention and treatment.

2. Methods

The content was searched from major online databases PubMed, ScienceDirect, Scopus and Google Scholar using keywords “Gallbladder cancer” and “GBC” in the period from year 2019 to 2024. Articles were selected as per the inclusion and exclusion criteria. Inclusion criteria involved the relevant clinical case studies, randomized controlled trials, experiments, longitudinal studies, epidemiologic studies and bioactivity studies. Exclusion criteria filtered the review articles, case analyses, theses, letters, editorials, articles of unavailable full text, and clinically problematic articles. The literature search published since 2019 resulted in 36 articles from PubMed, 51 from ScienceDirect, 177 from Scopus, and 723 from Google Scholar. A total of 987 articles were viewed, and manually filtered for the duplicates and no full text. Further filtering was made by reviewing abstracts and full text. The remaining articles were thoroughly reviewed wherein the primary filtering yielded 80 articles, and the secondary returned 12 articles. They were reviewed in full for the inclusion criteria including study subjects, methods and results (Fig. 1).

3. GBC epidemiology

GBC is a form of hepatobiliary malignancy arising from the mucosal lining of gallbladder. It is initially asymptomatic and tends to metastasize [16]. GBC is the 6th most prevalent cancer of gastrointestinal tract. Its earlier diagnosis is vital as it becomes more deadly with its later detection [17]. GBC has higher incidence in Southeast Asia. GBC is the 22nd most prevalent cancer worldwide with 219,420 new cases (1.2% of all malignancies) and 165,087 deaths (1.7% of cancer-related deaths) since 2018 [18]. Risk factors for GBC include gallstones, biliary cysts, carcinogens exposure, Helicobacter pylori infection, typhoid fever, abnormal pancreaticobiliary junction and genetic, gender, racial and geographic factors. Weight loss, vaccination, treatment against bacterial infections, early detection and removal are the preventive measures [19].

Gallstones and chronic cholecystitis are the frequent risk factors of developing GBC. Gallstones are associated with 95% of GBC cases [20]. A clinical case series of 228 GBC patients in China exhibited that more than half of the GBC patients were of 40–60 years age. Liver metastasis was predominant with 61.4% [21]. Men have higher incidence and risk of cancer because of sex-related biological factors. Only GBC and thyroid cancer have lower incidence rates in men compared to women [22]. GBC is the most prevalent cancer in Bolivia and Chile [4].

GBC prognosis has been poorer with age, large tumor size, adenocarcinoma, and advanced tumor stage, even with resection [23, 24]. GBC has 5-year survival rate of 82.7% for stage 1 and 73.4% for stage 2, despite being managed with adjuvant therapy [25]. Age is the common risk factor for GBC with poor prognosis in older patients after the surgery. This is associated with the improved odds of overall survival and cancer-specific survival in elderly patients [26–28]. GBC recurrence leads to the local disease recurrence. Its risk factors include jaundice, invasion to lymphatic vessels, or surgical T category 3/4 and N category 1/2 status [29, 30].

4. GBC prevention

The association between intramuscular adipose tissue content (IMAC), survival outcomes, and postoperative complications in GBC patients has good predictive value. IMAC is a novel marker of sarcopenia and reflection of skeletal muscle quality. It assists in recurrence, or disease and specific survival (DSS) analysis in cancer patients [31]. This muscle mass loss is associated with the changes in body composition. Preventing the accumulation of adipose tissue may reduce age-related conditions in later life. This is linked to the diet which suggests that healthy diet can have positive impact on body composition [32]. A healthy diet and obesity management are vital in preventing GBC, as found out in a meta-analysis study conducted on the association between bariatric surgery and future cancer prevention. The bariatric surgery did not reduce the incidence of esophageal, gastric, thyroid, kidney, prostate and multiple myeloma, however, it might reduce the future GBC incidence [33]. Gallbladder is a sac localized below the liver in human body. It is difficult to access bile and tissue sample. Bile is produced by the liver cells and released from gallbladder into the upper small intestine for facilitating fat’s digestion. The bile microbiome is associated with biliary inflammation and carcinogenesis [34]. Metagenomics from the perspective of microbial metabolomics has shown that it can alleviate symptoms in type 2 diabetes mellitus (T2DM) patients. This is attributed to its role in regulating short-chain fatty acid (SCFA) content in colon and promoting the glucagon-like peptide 1 (GLP-1) secretion [35–37]. GLP-1 is an agonist and approved drug for diabetes treatment. It is also used for weight loss. However, GLP-1 agonists usage is associated with increased gastrointestinal risks in diabetic patients, particularly the increased incidence of intestinal obstruction, pancreatitis, gastroparesis and biliary disease. These findings are supported by a randomized sample cohort study of 16 million patients [38–40].

5. GBC treatment

Treatments include surgery, adjuvant, palliative and targeted therapies. Surgery is an individualized approach of resection based on radiological findings. Personalized surgery considers patient’s condition and other factors [41]. It is used from GBC biological perspective as is the case in adjuvant therapy which considers age, type or stage of cancer and the side effects. However, there is a limitation [42]. Palliative therapies include gemcitabine and cisplatin combination chemotherapy as the first-line treatment [43]. Folinic acid (leucovorin) fluorouracil (5-FU) oxaliplatin (FOLFOX) chemotherapy is aggressive which improves GBC prognosis. Targeted therapies also include human epidermal growth factor receptor 2 (HER2/Neu; ErbB2), vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) and antiangiogenic therapy, epidermal growth factor receptor (EGFR; ErbB1; HER1), mitogen-activated protein kinase (MAPK; RAS/RAF/MEK/ERK)

pathway, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, programmed death-1/programmed death-ligand 1 (PD-1/PD-L1), microsatellite instability-high (MSI-High), high tumor mutational burden (TMB) and immune checkpoint inhibitor (ICI) therapy, DNA damage repair (DDR) deficiency, and other molecular alterations in GBC [44–46].

Recent therapeutic approaches for GBC in clinical cases of 2022–2024 had been based on the chemotherapy of neoplasms having genetic mutations (Table 1). Olaparib efficacy was reflected in the advanced cancers harboring pathogenic mutations (germline or somatic) of genes having role in homologous recombination (HR) [47, 48]. This was depicted in a cohort study of 27 patients with breast cancer gene 1 (*BRCA*1), breast cancer gene 2 (*BRCA*2), checkpoint kinase 2 (CHEK2) and ataxia telangiectasia mutated (ATM) mutations. The study population included pancreatic, gallbladder, pancreatic endocrine and parathyroid cancer patients [49–51]. The patients with *BRCA*1/2 mutations in all cancer types benefited from olaparib, except those with ATM and CHEK2. This confirmed the *BRCA*1/2 importance [52]. Originally, GBC treatment was limited [53]. It was found in a blinded, randomized, and case-control study that the reversible small molecule pan-epidermal growth factor receptor inhibitors, *i.e.*, varlitinib and capecitabine were effective as the second-line treatment of GBC [54–56]. A clinical trial of 21 patients demonstrated that the oral treatment with varlitinib and capecitabine was a positive therapeutic adjunct for GBC patients [57]. Most biliary tract cancer patients received palliative chemotherapy. Chemotherapy can shrink the tumor and allow surgical resection in early unresectable biliary tract cancer. Gemcitabine (GEM)-based chemotherapy had been effective in 12-patient clinical trial. This was compared with GEM monotherapy, and GEM and cisplatin combination (GEM + CDDP). Other GEM-based therapies included GEM and erlotinib combination (GEM-E), and substantial GEM dose combined with durvalumab (GEM-Durva) [58]. The antitumor efficacy of poly (adenosine diphosphate-ribose) polymerase (PARP) plus PD-L1 inhibition (olaparib + durvalumab, O + D) was demonstrated in a clinical case study of 48 O + D, 16 *BRCA*1/2, and

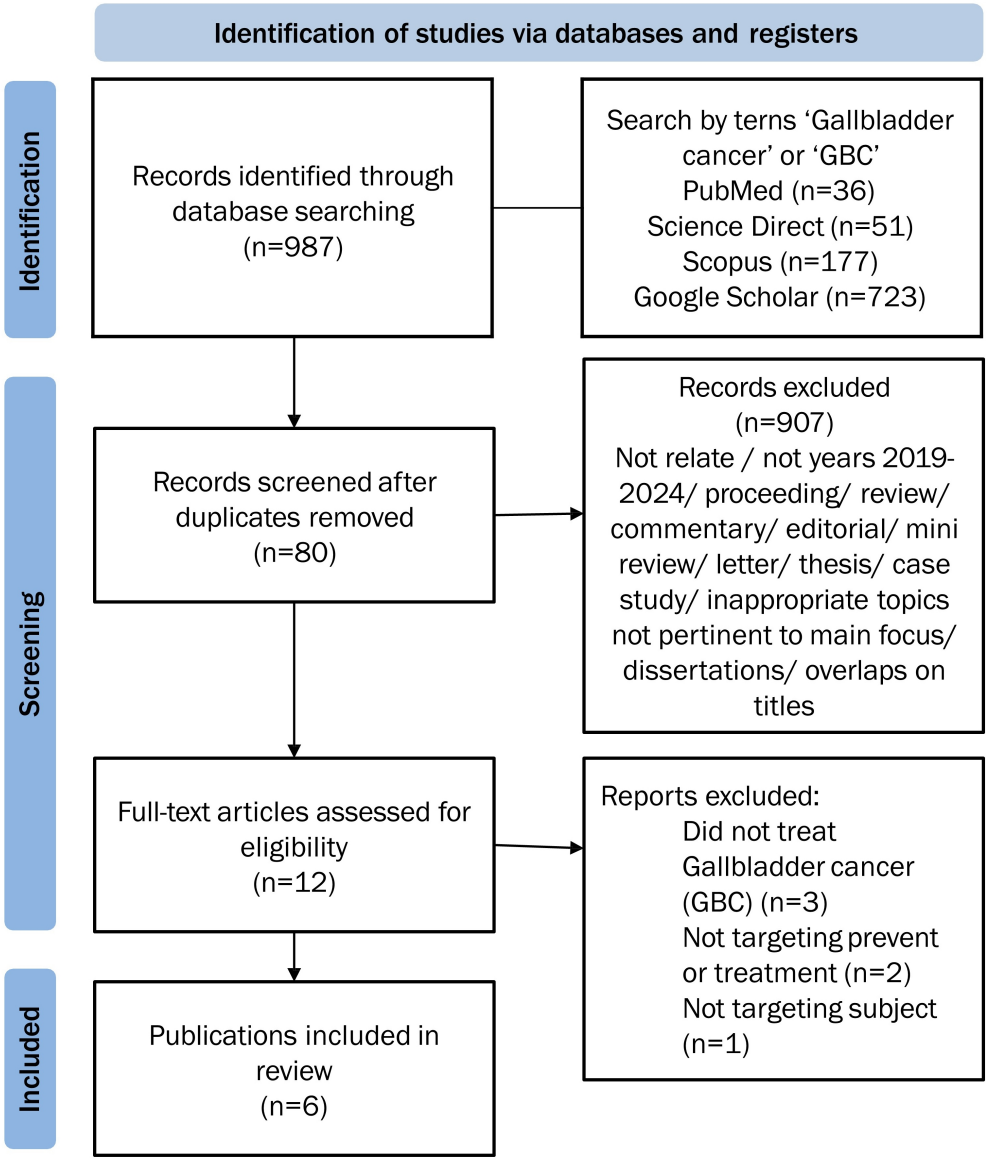

FIGURE 1. Flowchart of the articles' selection process.

TABLE 1. Clinical trials for GBC treatment.

Reference	Study Type According to Protocol	Subjects	Tools and Interventions	Outcomes
Chen *et al*. [41]	Factor-control study	First 13 somatic or germline mutation in the same gene patients, 14 additional patients included	Pathogenic mutation (germline or somatic) in a gene having role in HR	Efficient in variety of cancer types with somatic or germline mutations in *BRCA*1/2 genes
Joris *et al*. [52]	Randomized control trial	127 patients: Baricitinib + capecitabine (n = 64), placebo + capecitabine (n = 63)	Varlitinib and capecitabine, reversible small molecule pan-human epidermal growth factor receptor inhibitors	Second-line treatment with baricitinib + capecitabine was well tolerated. PFS benefit seen in female GBC patients
Nakachi *et al*. [53]	Factor-control study	48 patients treated with O + D: *BRCA*1/2 alterations (group 1, n = 16), HRR alterations (group 2, n = 32)	PARP + PD-L1 inhibition (olaparib + durvalumab, O + D)	Serves as a clinically meaningful therapeutic in several HRR-defective cancers including rare cancers
Javle *et al*. [54]	Repeated measures research design	28 adult GBC patients (≥18 years age)	FTD/TPI + irinotecan	Confirmed safety and efficacy of FTD/TPI and irinotecan in biliary tract cancer patients' refractory to gemcitabine-based therapy
Oh *et al*. [58]	Clinical trial	12 patients with early-stage unresectable biliary tract cancer	GEM, GEM + CDDP, GEM-E, GEM-Durva	Chemotherapy recommended for early unresectable biliary tract cancer in reducing tumor size and expanding indications
Thavaneswaran *et al*. [59]	Factor-control study	Patients (n = 128) received pemigatinib 1–20 mg once a day and intermittently (2 weeks on/1 week off, n = 70), or continuously (n = 58)	Part 1 (dose escalation, 3 + 3 design), Part 2 (dose escalation) is a two-stage treatment recommended for tumors with or associated with FGF/FGFR activity	Safety and clinical activity of pemigatinib (from FGFR), Response by FGFR fusions/rearrangements, and mutations in multiple tumors

GBC, Gallbladder cancer; HR, Homologous recombination; PFS, Progression-free survival; O + D, Olaparib + durvalumab; PARP, Poly (ADP-ribose) polymerase; FTD/TPI, Trifluridine/tipiracil; FGF, Fibroblast growth factor; GEM, Gemcitabine; GEM + CDDP, Combination of GEM and cisplatin; GEM-E, Combination of GEM and erlotinib; GEM-Durva, GEM combined with durvalumab; FGFR, Fibroblast growth factor receptor; BRCA, breast cancer gene; PD-L1, Programmed death-ligand 1; HRR, homologous recombination repair.

32 homologous recombination repair (HRR) patients. O + D had therapeutic potential because of the antitumor activity in GBC including rare cancers. The O + D combination had a confirmed safety profile with no toxicity concerns. It also had the clinically meaningful progression-free survival (PF) 56 rates in several cancers with HRR defects [59].

New therapeutic agents evolving from previous treatments had also been investigated. A clinical case series of 28 adult patients confirmed the therapeutic efficacy of trifluridine/tripiracil (FTD/TPI) and irinotecan for gastrointestinal malignancies. FTD/TPI as the second-line treatment was evaluated for safety in repeated studies until the toxicity appeared. The safety and efficacy of FTD/TPI + irinotecan was demonstrated in patients with gallbladder and biliary tract cancer refractory to previously used gemcitabine-based therapy [60]. Pemigatinib as a fibroblast growth factor receptor (FGFR) 1–3 inhibitor had exhibited safety, pharmacokinetics, and anti-cancer activity in refractory malignancies. This was confirmed in a clinical trial of 128 patients taking pemigatinib orally. There was no toxicity at pharmacologically active dose of 24 mg. It was the most effective in bile duct and gallbladder cancers. It also had positive impact on broader tumor spectrum including head and neck, pancreatic, uterine, urothelial, recurrent phyllodes cell, non-small cell and lung cancers [61].

6. Conclusions

GBC research is crucial as it has no specific symptoms and lack information on specific treatment or prevention strategies. GBC prevention begins with weight control and healthy diet as is the case with type 2 diabetes treatment. GBC is commonly treated with surgical resection of tumor, however, new treatment strategies are being designed based on chemotherapy and genetic modifications. The health promotion considerations also include personalized strategies by catering the individual characteristics of patients. Clinical trials on prevention and treatment strategies for GBC should thus be designed. New therapeutic strategies and methods must be developed based on these studies and the GBC characteristics.

ABBREVIATIONS

5-FU, fluorouracil; ATM, ataxia telangiectasia mutated; BRCA, breast cancer gene; CHEK2, checkpoint kinase; DDR, DNA damage repair; EGFR/ErbB1/HER1, epidermal growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid (leucovorin) fluorouracil (5-FU) oxaliplatin; FTD/TPI, trifluridine/tripiracil; GBC, gallbladder cancer; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HER2/Neu; ErbB2, human epidermal growth factor receptor 2; HR, homologous recombination; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; IMAC, intramuscular adipose; MAPK, mitogen-activated protein kinase; MSI-High, microsatellite instability-high; O + D, olaparib + durvalumab; PARP, poly (adenosine diphosphate-ribose) polymerase; PD-1/PD-L1, programmed death-1/programmed death-ligand 1; PF, progression-free survival; PFS, progression-free survival; PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; SCFA, short-chain fatty acid; GLP-1, glucagon-like peptide 1; T2DM, type 2 diabetes mellitus; TMB, high tumor mutational burden; VEGF/VEGFR, vascular endothelial growth factor/vascular endothelial growth factor receptor.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YP and KHK—conceptualization, vali-dation, writing-review. YP—methodology, software, formal analysis, investigation, resources, data curation, writing-original draft preparation, editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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