Review Article

Long Noncoding RNA UCA1 in Gastrointestinal Cancers: Molecular Regulatory Roles and Patterns, Mechanisms, and Interactions

Suaidah Ramli 1, Maw Shin Sim 1, Rhanye M. Guad 2, Subash C. B Gopinath 3,4, Vetriselvan Subramaniyan 5, Shivkanya Fuloria 6, Neeraj K. Fuloria 6, Ker Woon Choy 7, Sohel Rana 8, and Yuan Seng Wu 9

1Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, University of Malaya, Kuala Lumpur 50603, Malaysia
2Department of Biomedical Science and Therapeutics, Faculty of Medicine and Health Science, Universiti Malaysia Sabah, Kota Kinabalu 88400, Sabah, Malaysia
3School of Bioprocess Engineering, Universiti Malaysia Perlis, Arau 02600, Perlis, Malaysia
4Institute of Nano Electronic Engineering, Universiti Malaysia Perlis, Kangar 01000, Perlis, Malaysia
5Department of Pharmacology, School of Medicine, Faculty of Medicine, Bioscience and Nursing, MAHSA University, Jenjarom, Selangor 42610, Malaysia
6Faculty of Pharmacy, AIMST University, Bedong, Kedah 08100, Malaysia
7Department of Anatomy, Faculty of Medicine, Universiti Teknologi MARA, Shah Alam, Sungai Buloh 47000, Selangor, Malaysia
8Department of Pharmacy, Faculty of Biological Science and Technology, Jashore University of Science and Technology, Jashore-7400, Bangladesh
9Department of Biochemistry, School of Medicine, Faculty of Medicine, Bioscience and Nursing, MAHSA University, Jenjarom, Selangor 42610, Malaysia

Correspondence should be addressed to Yuan Seng Wu; sengwu_21@yahoo.com

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The rising trend of gastrointestinal (GI) cancer has become a global burden due to its aggressive nature and poor prognosis. Long noncoding RNAs (lncRNAs) have recently been reported to be overexpressed in different GI cancers and may contribute to cancer progression and chemoresistance. They are featured with more than 200 nucleotides, commonly polyadenylated, and lacking an open reading frame. LncRNAs, particularly urothelial carcinoma-associated 1 (UCA1), are oncogenes involved in regulating cancer progression, such as cell proliferation, invasion, migration, and chemoresistance, particularly in GI cancer. This review was aimed to present an updated focus on the molecular regulatory roles and patterns of lncRNA UCA1 in progression and chemoresistance of different GI cancers, as well as deciphering the underlying mechanisms and its interactions with key molecules involved, together with a brief presentation on its diagnostic and prognostic values. The regulatory roles of lncRNA UCA1 are implicated in esophageal cancer, gastric cancer, pancreatic cancer, hepatobiliary cancer, and colorectal cancer, where they shared similar molecular mechanisms in regulating cancer phenotypes and chemoresistance. Comparatively, gastric cancer is the most intensively studied type in GI cancer. LncRNA UCA1 is implicated in biological roles of different GI cancers via interactions with various molecules, particularly microRNAs, and signaling pathways. In conclusion, lncRNA UCA1 is a potential molecular target for GI cancer, which may lead to the development of a novel chemotherapeutic agent. Hence, it also acts as a potential diagnostic and prognostic marker for GI cancer patients.
1. Introduction

Gastrointestinal (GI) cancer has become one of the major challenges in the health sector in recent decades. GI cancer is a group of cancers that affect the GI tract, such as esophagus, stomach, gallbladder, liver, biliary tract, small intestine, and large intestine [1, 2]. In 2018, GI cancer contributed 26% among all cancer cases and 35% of cancer-causing death worldwide [3]. There are five major GI cancers, namely, gastric cancer (GC), hepatobiliary cancer, esophageal cancer (EC), pancreatic cancer (PC), and colorectal cancer (CRC), accounting for approximately 1 million, 840,000, 570,000, 460,000, and 1.7 million new cases were reported in 2018, respectively [4]. Comparatively, EC, GC, and liver cancer (LC) are predominant in Asian population, whereas CRC shows more incidence in Europe and North America [3]. Apart from that, GI cancer shows a reduced 5-year survival rate and a poor prognosis at the late stage of cancer [5]. Generally, several factors have been reported to be the contributing risk factors for GI cancer, including tobacco smoking, alcohol consumption, diet, and obesity and infectious, such as Helicobacter pylori in GC and hepatitis virus in LC [3, 6, 7].

With the recent advancement in RNA sequencing technology transcriptome knowledge, there are increased interests in long noncoding RNAs (lncRNAs) as they play an important role in tumorigenesis, particularly gene regulation [8, 9]. LncRNA is characterized by possessing more than 200 nucleotides that would not be translated into protein [10]. It can be found in both nucleus and cytoplasm where the chromatin remodeling, transcriptional regulation, and RNA processing take place in the nucleus, while its interaction with mRNA and signaling pathway occurs in the cytoplasm [11, 12]. One of the reported cancer-related lncRNAs is urothelial carcinoma-associated 1 (UCA1) that was first discovered in 2006 as it was found to be overexpressed in bladder cancer (BC) cells, a cancer close to but not belonged to GI cancer [13]. It belongs to human endogenous retrovirus H family and is located at 19p13.12 of the chromosomes positive-strand with three exons and two introns [13]. To date, three LncRNA UCA1 isoforms produced by RNA splicing have been discovered, and each of them with different sizes, including 1.4, 2.2, and 2.7 kb [14, 15]. Among them, 1.4 kb LncRNA UCA1 is the most assessed and abundant isoform, while 2.2 kb isoform is relatively more participated in chemoresistance [14]. For instance, Wang et al. showed that LncRNA UCA1 significantly associated with cancer chemoresistance toward cisplatin, gemcitabine, 5-fluorouracil, tamoxifen, and imatinib. Interestingly, the chemosensitivity of these drugs was significantly increased when LncRNA UCA1 was silenced [16].

Apart from these, LncRNA UCA1 has been detected to be overexpressed in various cancers, particularly GI cancers, such as CRC, esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC), and GC [17–19]. Among lncRNAs, LncRNA UCA1 has been demonstrated to have significant regulatory roles in cancer progression, including cell proliferation, invasion, migration and metastasis, and chemoresistance in BLS-211 BC cells [13]. In the last decade, the regulatory roles of lncRNAs have been intensively investigated in which most studies have suggested that the mechanistic pathways underlying the regulatory roles of LncRNA UCA1. In this context, its interaction with the key genes or proteins is the key causative factor that leads to the development of GI cancer.

Therefore, this review aims to provide a detailed insight into the regulatory roles of LncRNA UCA1 in GI cancer progression and chemoresistance, as evidenced in preclinical and clinical studies. In addition, it also discusses various molecular mechanisms underlie and the key molecules involved, intending to present its potential as a novel molecular target, as well as a diagnostic and prognostic marker for GI cancer.

2. LncRNA UCA1

Over the past few years, there is a bloom of transcriptome studies associated with the advancement in RNA sequencing technology, which enables the view of the complexity of eukaryotic gene expression [20]. This advanced technology leads to the discovery of lncRNAs [21]. More than 98% of the genomes transcribed into ncRNAs are categorized, either as structural RNAs or regulatory RNAs, where LncRNA is classified under regulatory RNAs [22]. LncRNAs are discovered as an important new player in cell differentiation and development, as well as organogenesis and genomic imprinting [23, 24]. Additionally, most lncRNAs, including LncRNA UCA1, are much like mRNAs where they are transcribed by RNA polymerase II with similar chromatin states to mRNAs, and they usually 5′ capped, spliced, and polyadenylated [25, 26]. The biogenesis of LncRNA UCA1 is illustrated in Figure 1.

It has been reported that several LncRNAs participate in the special processing events, including DNA organization. In this event, genomic DNA is packed in the nucleus with a special genomic organization, depending on both histone and chromatin modifications that are regulated by epigenetic complexes and affect the transcriptional activity [27, 28]. For instance, LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and LncRNA nuclear enriched abundant transcript 1 (NEAT1) are localized at the nuclear speckles and nuclear paraspeckles, respectively, after processing at 3′ ends by RNA polymerase II to form RNA-like small RNA products and mature lncRNAs [25, 29, 30]. However, the exact DNA organization for LncRNA UCA1 remains to be confirmed. Functionally, LncRNAs are involved in chromatin and epigenetic modifications [31, 32]. LncRNA UCA1 also acts as an miRNA decoy and miRNA sponge, which sequester miRNA intracellularly and compete with other genes for miRNA binding, leading to an increased level of miRNA target gene expression [1, 33].

Furthermore, LncRNA has also shown to play an important role in embryogenesis where it has been identified to be upregulated after 28 weeks of gestational in the tissue of heart, urinary bladder, and uterus, but downregulation is detected in liver, kidney, lung, spleen, intestine, stomach, skin, and cervix. In adult tissues, LncRNA UCA1 expression
is relatively conserved at a low expression level, except for heart, spleen, and placenta [34]. In short, the ideal expression of lncRNA UCA1 is remarkably essential for cell growth and development, particularly in embryogenesis stage.

3. Molecular Regulatory Roles, Patterns, Mechanisms, and Interactions of LncRNA UCA1 in Different Gastrointestinal Cancers

It has been reported that high expression levels of lncRNA UCA1 are detected in GI cancer cells [35, 36]. Thus, lncRNAs may play an important role for GI tumorigenesis. The positive association of lncRNA UCA1 with the overall survival of GI cancer patients was revealed in a meta-analysis [35]. The pooled result of 14 studies indicated that poor overall survival in patients with digestive malignancies was associated with lncRNA UCA1 overexpression [35]. Since then, different studies were conducted to further discover the association between GI cancer and lncRNA UCA1 as well as identify the possible mechanisms responsible for GI cancer progression. In this review, the expression pattern, regulatory roles and patterns, mechanistic pathways, and interactions of key molecules that are associated with lncRNA UCA1 in GI cancer progression and chemoresistance, including EC, GC, hepatobiliary cancer, PC, and CRC, are summarized (Table 1). A brief insight of the potential role of lncRNA UCA1 as a diagnostic and prognostic marker, wherever applicable in different GI cancers, is also presented. The interaction of lncRNA UCA1 that affects the target gene expression of miRNAs and activation of pivotal signaling pathway are illustrated in Figures 2 and 3, respectively.

3.1. Esophageal Cancer. In ESCC patients, the most predominant deadly types of EC, lncRNA UCA1 has been reported to be overexpressed and contributed to poor prognosis [37]. Jiao et al. showed that lncRNA UCA1 was strongly associated with EC cell proliferation by functioning as a competing endogenous RNA (ceRNA) to regulate the expression of Sry-related high-mobility group box 4 (Sox4), a target protein of lncRNA UCA1 [38]. Additionally, lncRNA UCA1 also can directly interact with miR-204 to reduce miR-204-mediated Sox4 degradation; thus, Sox4 can exert its biological role as a tumor-promoting protein to stimulate EC progression [38]. Apart from that, overexpressed lncRNA UCA1 could also promote cell proliferation and metastasis by enhancing aerobic glycolysis through Warburg effect [39]. These happened when lncRNA UCA1 sequestered miR-203, which then increased the levels of hexokinase 2 (HXX2) [39].

Despite several studies have reported a positive correlation between overexpressed lncRNA UCA1 and tumor progression; however, contradictory findings were reported. For instance, Wang et al. discovered that overexpression of lncRNA UCA1 suppressed ESCC cell growth via the inhibition of Wnt signaling pathway by suppressing β-catenin activity [40]. They claimed that lncRNA UCA1 could reduce the expression of active β-catenin protein expression in the cell nucleus and myelocytomatisis proto-oncogene (C-myc), which is a target protein of Wnt signaling pathway in regulating cell cycle. This action ultimately reduced cancer cell proliferation, migration, and invasion [40]. Similarly, Zhu et al. also demonstrated that lncRNA UCA1 was lowly expressed in EC tissues and plasma exosomes, which is a lipid-bilayer extracellular vesicle used as a cargo system for various molecules, including lncRNAs, for implicating in the pathogenesis of many diseases, including cancer, by regulating intercellular communication. They specifically found that exosomal lncRNA UCA1 could act as a growth inhibitor in EC as its overexpression inhibited cell proliferation, migration, invasion, and colony formation significantly, as well as tumor growth in vivo via direct targeting of high levels of miR-613 [41]. It also acts as a potent diagnostic biomarker for EC, with great sensitivity (86.7%) and specificity (70.2%) [41]. However, these findings need to be further assessed as there is increasing evidence showing that lncRNA UCA1 acts as an oncogenic lncRNA instead of having tumor-suppressing function. Taken together, further molecular studies of lncRNA UCA1 should be conducted to elucidate its associated molecular mechanisms of regulatory roles in EC clearly.

3.2. Gastric Cancer. GC is one of GI cancers that contribute to high mortality due to late diagnosis [3, 77]. Intriguingly, Gao et al. suggested that lncRNA UCA1 could be a potential diagnostic and biomarker target in the early stage of GC, owing to the fact that highly expressed lncRNA UCA1 can be easily found in the plasma of GC patients and therefore provides simplicity for sample extraction [42]. Similarly, it has also been discovered that lncRNA UCA1 is overexpressed in both GC tumor and cell lines [43]. Moreover, it was also reported to play a role in GC cell migration and invasion via the induction of epithelial-mesenchymal transition (EMT) by competitively binding to miR-203, increasing the expression of its target protein, Zinc Finger E-Box Binding Homebox 2 (ZEB2) [44].

In addition to miR-203, lncRNA UCA1 also interacts with miR-495-3p, supporting the role of UCA1 acting as a ceRNA [45]. Sun et al. reported that lncRNA UCA1 expression could be regulated by special AT-rich-binding protein 1 (SATB1), which was involved in chromatin modification in both MKN-45 and BGC-823 GC cells [45]. However, lncRNA UCA1 only regulated the protein levels of SATB1 in MKN-45 GC cells but not in BGC-823 cells [45]. Thus, further investigation is required to discover the rationale for obtaining such findings.

Similarly, lncRNA UCA1 has also found to regulate miR-590-3p expression that results in the activation of cAMP-responsive element-binding protein 1 (CREB1), which is an oncogenic protein [46]. In addition, it plays a role in suppressing the immune system of GC cells by elevating the expression of programmed death-1 ligand-1 (PDL1) via sponging miR-193a and miR-214 [47]. In addition, Wang et al. also reported that lncRNA UCA1 could sponge other miRNAs, for instance, miR-26a and miR-26b, thereby reducing their expression levels [47].
This finding indicated that lncRNA UCA1 could function as an miRNA sponge to reduce miRNA expression in the cells, subsequently reducing its inhibitory effects on the target protein. On the other hand, reduced ki-67 protein levels and increased levels of cleaved poly (ADP-ribose) polymerase 1 (PARP1) and cleaved caspase 3 were observed in GC cells after lncRNA UCA1 silencing [47]. However, the exact mechanism of lncRNA UCA1 in regulating ki-67, PARP1, and caspase 3 is unknown, and further confirmation is required, particularly in identifying miRNAs or proteins associated with the regulation of lncRNA UCA1.

In addition, Zuo et al. demonstrated that the induction of high lncRNA UCA1 expression in GC cells was mediated by transforming growth factor β1 (TGF-β1) [48]. The overexpressed lncRNA UCA1 consequently promoted EMT by regulating the expression levels of EMT-related proteins, such as E-cadherin, vimentin, snail, and zonula occludens-1 (ZO-1) [48]. For instance, the mRNA levels of epithelial cell markers, such as E-cadherin and ZO-1, were reduced, while an elevation was observed for mesenchymal cell markers, namely vimentin and snail [48]. This finding indicated that apart from regulating other genes or proteins, lncRNA UCA1 also can be regulated by other genes or proteins.

Meanwhile, lncRNA UCA1 has also been reported to regulate phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (p-mTOR), and ribosomal protein S6 kinase (S6K), while reducing the eukaryotic translation initiation factor 4E (EIF4E) protein levels in GC cells [49]. Consequently, the regulation of these proteins promoted GC cell growth and proliferation [49]. This finding showed that lncRNA UCA1 could regulate multiple proteins involved in a signaling pathway.

On the other hand, Wang et al. reported that specificity protein 1 (SP1) promoted the expression of lncRNA UCA1 in GC cells by binding to the core promoter of UCA1 [50]. The expressed lncRNA UCA1 was then activated AKT/GSK-3β/cyclin D1 axis by interacting with enhancer of zeste homolog 2 (EZH2), a histone methyltransferase [50]. Meanwhile, the interaction of lncRNA UCA1 enhanced EZH2 expression, which subsequently elevated the expression of cyclin D1 to promote cell cycle [50]. These findings supported the previous hypothesis that the association of lncRNA UCA1 in regulating other genes via epigenetic modification, which is histone modification in this case. The association of lncRNA UCA1 with AKT/GSK-3β/cyclin D1 was also identified in HCC [60].

In addition to EMT, lncRNA UCA1 can induce GC metastasis by regulating G protein-coupled receptor kinase 2 (GRK2) degradation and Casitas B-lineage Lymphoma (Cblc)-mediated ubiquitination, resulting in the activation of extracellular-signal-regulated kinase (ERK)/matrix metalloproteinase-9 (MMP-9) signaling pathway [51]. Wang et al. demonstrated that lncRNA UCA1 interacted with GRK2 and led to the exposure of GRK2 ubiquitination sites toward Cblc for its degradation [51]. Consequently, the degraded GRK2 activated ERK/MMP-9 signaling pathway, which increased MMP-9 protein levels, to promote cell membrane degradation, facilitating cancer cell migration and invasion [51]. This finding showed that lncRNA UCA1 could regulate the level of another protein by direct binding for degradation.

lncRNA UCA1 also plays a prominent role in chemoresistance via miRNA signaling. For instance, the silenced lncRNA UCA1 could upregulate the mRNA levels of miR-27b and lead to reduced IC₅₀ of doxorubicin, cisplatin, and 5-fluorouracil, as well as promoting doxorubicin-induced apoptosis in doxorubicin-resistance SGC-7901 GC cells [52]. In other words, the reduction of lncRNA UCA1 expression could improve the chemosensitivity of chemotherapeutic agents, at least for doxorubicin, cisplatin, and 5-fluorouracil in GC therapy. Correspondingly, Cheng et al. reported that lncRNA UCA1 silencing enhanced GC chemosensitivity toward cisplatin by regulating the expression of miR-513a-3p and Cytochrome P450 1B1 (CYP1B1) [53].

Chemosensitivity is also affected by cancer microenvironment, such as hypoxic microenvironment, that claims to block the exposure of chemotherapeutic agents to cancer cells [54]. Yang et al. reported that GC cells could survive in the hypoxic environment via the interaction of lncRNA UCA1 with miR-7-5p, elevating the expression of epidermal growth factor receptor (EGFR) in hypoxia-resistant GC cells [54]. Nonetheless, chronic hypoxia environment with a slight increment in the protein levels of hypoxia-inducible factor-1alpha (HIF-1α) could reduce lncRNA UCA1 expression [54]. Taken together, these findings demonstrated
<table>
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<tr>
<th>Cancer type</th>
<th>Study subject</th>
<th>Cell line</th>
<th>Finding/mechanistic response</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Esophageal cancer</td>
<td>90 ESCC patients who underwent surgery</td>
<td>EC109, EC9706, KYSE150, KYSE510, and NE1</td>
<td>(i) LncRNA UCA1 was overexpressed and contributed to poor prognosis (ii) Silenced lncRNA UCA1 decreased cell proliferation, migration, and invasion (iii) LncRNA UCA1 was overexpressed and contributed to poor prognosis</td>
<td>[37]</td>
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<td></td>
<td>66 esophageal cancer patients underwent surgical resection</td>
<td>EC9706 and KYSE</td>
<td>(i) LncRNA UCA1 was overexpressed and contributed to poor prognosis (ii) Sox4 was identified as a direct target gene of lncRNA UCA1 and acted as a ceRNA (iii) LncRNA UCA1 reduced miR-204 level</td>
<td>[38]</td>
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<tr>
<td>Gastric cancer</td>
<td>110 EC tissues and 60 paired of adjacent nontumorous tissues</td>
<td>EC1, EC109, EC9706, KYSE150, and Het-1A</td>
<td>(i) LncRNA UCA1 was overexpressed in EC tissues with advanced EC stages and was associated with poor prognosis (ii) Overexpressed lncRNA UCA1 promoted cell proliferation and metastasis (iii) LncRNA UCA1 promoted glycolysis by sequestering miR-203 to increase HK2 levels, resulting in enhanced Warburg effect</td>
<td>[39]</td>
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<td></td>
<td>106 newly diagnosed patients with primary cancer and previously untreated ESCC</td>
<td>EC109</td>
<td>(i) LncRNA UCA1 lowly expressed in tumor tissue compared to the adjacent nontumor tissue (ii) LncRNA UCA1 suppressed ESCC via inhibition of Wnt signaling pathway (iii) LncRNA UCA1 reduced C-myc and active β-catenin protein expression</td>
<td>[40]</td>
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<td>15 paired EC tissues and adjacent normal tissues of EC patients</td>
<td>EC18, KYSE140, and NEEC</td>
<td>(i) LncRNA UCA1 expression was decreased in EC tissues and plasma exosomes (ii) LncRNA UCA1 inhibited cell proliferation, invasion, migration, and colony formation as well as inhibited tumor growth in vivo (iii) Exosomal lncRNA UCA1 directly targeted miRNA-613 in EC cells</td>
<td>[41]</td>
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<td>20 plasma samples of patients and pair-matched plasma samples</td>
<td>Five GC tissues and five pair-matched noncancerous tissues</td>
<td>(i) Overexpressed lncRNA UCA1 in both GC tissue and plasma of GC patients (ii) Plasma lncRNA UCA1 provided higher diagnostic performance for the detection of GC</td>
<td>[42]</td>
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<td>Cancer type</td>
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<td>112 patients diagnosed with GC</td>
<td>SGC-7901, BGC-823, MKN-28, AGS, and GES-1</td>
<td>(i) Overexpressed lncRNA UCA1 in GC human tissue and GC cell lines</td>
<td>[43]</td>
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<td></td>
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<td>(ii) High lncRNA UCA1 expression correlated with worse differentiation, tumor size, invasion depth, and TNM stage</td>
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<td>(i) Elevated lncRNA UCA1 in tumor tissues of GC patients</td>
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<td>Chinese patients</td>
<td>BGC-823 and SGC-7901</td>
<td>(ii) LncRNA UCA1 promoted metastasis by sponging miR-203, resulting in ZEB overexpression</td>
<td>[44]</td>
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<td>Ten GC and ten paracancerous normal tissues from the patients in China</td>
<td>MGC-803, SGC-7901, BGC-823, AGS, MKN-45, and GES-1</td>
<td>(i) LncRNA UCA1 expression was higher in GC compared to paracancerous tissues</td>
<td>[45]</td>
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<td>62 GC patients who underwent surgical resection</td>
<td>AGS, MKN-28, SGC-7901, MKN-45, and GES-1</td>
<td>(i) LncRNA UCA1 expression was higher in GC compared to paracancerous tissues</td>
<td>[46]</td>
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<td>40 primary GC tissues and corresponding adjacent nontumorous gastric tissue samples</td>
<td>AGS, SGC-7901, BGC-823, MGC-803, and SNU-1</td>
<td>(ii) LncRNA UCA1 repressed miR-590-3p, leading to increased CREB1 expression</td>
<td>[47]</td>
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<td>37 paired GC tissues and corresponding adjacent normal tissues</td>
<td>HGC27, MG-803, NCI-N87, BGC-823, SGC-7901, and GES-1</td>
<td>(iii) LncRNA UCA1 repressed miR-26a/b, miR-193a, and miR-214 expression through direct interaction</td>
<td>[48]</td>
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<td>Gastric cancer</td>
<td>MKN-28, SGC-7901, MGC-803, BGC-823, MKN-45, and GES-1</td>
<td>(i) Overexpressed lncRNA UCA1 in GC human tissue compared to adjacent noncancerous tissues</td>
<td>[49]</td>
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<td>102 gastric cancer patients who underwent surgery</td>
<td>AGS, SGC-7901, AGS, MKN-45, NCI-N87, and MKN-28</td>
<td>(ii) TGFβ1-induced lncRNA UCA1 elevation and acceleration of EMT</td>
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<td>39 patients with GC</td>
<td>MGC-803, HGC-27, NCI-N87, and GES-1</td>
<td>(i) The overexpression of UCA1 in GC was higher in GC tissue than adjacent noncancerous tissues, and it is correlated with TNM stage and lymph node metastases</td>
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<td>49 patients with GC</td>
<td>MGC-803, HGC-27, NCI-N87, and GES-1</td>
<td>(ii) LncRNA UCA1 highly expressed in GC tissues than its adjacent noncancerous tissues</td>
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<td>28 primary GC patients who had not received previous chemotherapy or radiotherapy</td>
<td>SGC-7901, SGC-7901, SGC-7901/ADR, SGC-7901/DDP, and SGC-7901/FU</td>
<td>(i) LncRNA UCA1 was highly expressed in GC tissues than its adjacent noncancerous tissues</td>
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<td>53 pairs of GC tissues and adjacent normal tissues</td>
<td>GES-1, SNU-5, AGS, and NCI-N87</td>
<td>(ii) Multidrug resistance of GC by repressing miR-27b</td>
<td>[52]</td>
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<td>(i) LncRNA UCA1 was highly expressed in GC tissues than its adjacent noncancerous tissues</td>
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<td>(iii) LncRNA UCA1 reduced miR-513a-3p and elevated CYP1B1</td>
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<td>(i) LncRNA UCA1 promoted the migration of hypoxia-resistant GC cells via miR-7-5p/EGFR axis</td>
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| Hepatobiliary cancer | 60 paired tumors and adjacent nontumorous liver tissues obtained immediately after surgical resection | LO2 cells and HBx-expressing hepatoma cells | (i) HBx induced lncRNA UCA1 expression in hepatocytes  
(ii) LncRNA UCA1 reduced p27kip1 expression and increased EZH2 expression via histone methylation on p27kip1 promoter region  
(iii) LncRNA UCA1 induced CDK2 expression without altering CDK4 and CDK6 | [55] |
|                  | 88 HCC patients                                                              | HepG2 and Huh7                   | (i) LncRNA UCA1 highly expressed in 79 patients out of 88 HCC patients  
(ii) TGF-β1 induced the expression of LncRNA UCA1 and HXK2  
(i) Overexpressed LncRNA UCA1 was detected in HCC tissues compared to healthy tissues  
(ii) miR-124 repressed ROCK1  
(iii) ROCK1 reduced LncRNA UCA1 expression  
(iv) HBV and HCV infections did not affect the expression of LncRNA UCA1 and miR-124 | [56] |
|                  | 66 newly diagnosed HCC patients                                              | SNU-398 and SNU-449              | (i) Overexpressed SND1 in HCC tissues than normal tissues  
(ii) SND1 induced LncRNA UCA1 expression through the interaction of SND1 with MYB  
(iii) Arsenic stress induced LncRNA UCA1  
(ii) LncRNA UCA1 promoted protective roles of arsenic-induced cell death by blocking autophagic flux  
(iii) LncRNA UCA1 protected HCC cells against arsenic stress by repressing miR-184 and elevating OSGIN1 that activated mTOR/p70S6K autophagy inhibition pathway | [57] |
|                  | 50 HCC patients from online data sets                                         | HEK 293t and HepG2               | (i) High expression of lncRNA UCA1 was associated with tumor size, lymph node metastasis, TNM stage, and short survival time in BGC patients  
(ii) Recruitment of EZH2 to the promoter of p21 and E-cadherin  
(iii) Epigenetically suppressed p21 and E-cadherin expression | [58] |
|                  | —                                                                            | HepG2                            |                                                                                      |           |
|                  | 68 CCA patients                                                              | HCCC-9810, RBE, QBC939, Huh-28, HuCCT1, KBMBC, CCLP-1, and HIBEC | (i) LncRNA UCA1 was overexpressed in CCA tissues and cell lines  
(ii) LncRNA UCA1 inhibited apoptosis through Bcl-2/caspase-3 pathway  
(iii) Activated AKT/GSK-3β axis elevated CCND1 expression | [59] |
|                  | 22 CCA patients receiving surgical resection                                 | LIPF155C, CCLP1, QBC939, huh28, and HIBEC | (i) LncRNA UCA1 was highly expressed lncRNA in CCA compared with paracarcinoma tissues  
(ii) Regulation of miR-122/CLIC1 and activation of ERK/MAPK signaling pathway | [60] |
| Pancreatic cancer | 45 GBC tissues and neighboring noncancerous tissues from patients who underwent liver resection | NOZ and GBC-SD                   | (i) High expression of lncRNA UCA1 was associated with tumor size, lymph node metastasis, TNM stage, and short survival time in GBC patients  
(ii) Recruitment of EZH2 to the promoter of p21 and E-cadherin  
(iii) Epigenetically suppressed p21 and E-cadherin expression | [61] |
|                  | 128 PC patients received operation as initial systemic treatment              | Panc-1, Bxpc-3, Capan-1,SW-1990, and HPD6Bc-7 | (i) LncRNA UCA1 overexpressed in PC tissue and cell lines  
(ii) LncRNA UCA1 suppressed p27 protein  
(iii) Highly expressed LncRNA UCA1 in PC tissues and cell lines  
(iv) LncRNA UCA1 sponged miR135a | [62] |
|                  | 50 PC patients                                                               | SW1990, Bxpc-3, MiaPaCa-2, PANC-1, Capan-1, and HPDE | (i) Out of 19 lncRNAs, LncRNA UCA1 was one of the overexpressed lncRNAs in PC tissues  
(ii) LncRNA UCA1 repressed miR-96, resulting in increased FOXO3 expression  
(iii) LncRNA UCA1 sponged miR135a  
(iii) LncRNA UCA1 overexpressed in PDAC tumor specimens than normal tissue  
(iv) LncRNA UCA1 promoted cell migration and invasion via Hippo signaling pathway | [63] |
|                  | 36 PC patients underwent surgical resection                                   | HPC-Y5, PANC-1, SW1990, and AsPc-1 | (i) Higher mRNA levels of LncRNA UCA1 in PC tissues than normal pancreatic tissues and correlated with poor prognosis  
(ii) LncRNA UCA1 sponged miR-135a  
(iii) LncRNA UCA1 promoted cell migration and invasion via Hippo signaling pathway | [64] |
|                  | Analysis of mRNA levels of LncRNA UCA1 in PC patients from BADEA and TCGA databases | BxPC-3, SW1990, PaTu8988, and PANC-1 | (i) LncRNA UCA1 sponged miR-590-3p  
(ii) LncRNA UCA1 acted as a ceRNA to increase the expression of KRAS via sponging miR-590-3p | [65] |
|                  | Analysis of LncRNA UCA1 mRNA levels from TCGA database in PDAC tumor specimens and normal | PaTu8902, Mpanc96, HEK293T, and H6C7 | (i) LncRNA UCA1 was highly expressed in PDAC tumor specimens than normal tissue  
(ii) LncRNA UCA1 sponged miR-135a  
(iii) KRAS promoted LncRNA UCA1 expression. | [66] |
<table>
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<tr>
<th>Cancer type</th>
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<td>Colorectal cancer</td>
<td>Two CRC cohorts, including 90 and 119 human primary CRC tissues and their paired adjacent noncancerous tissues, respectively</td>
<td>CaCO-2, SW480, HCT116, LoVo, and CCC-HIE-2</td>
<td>(i) Overexpressed lncRNA UCA1 promoted cell proliferation, apoptosis, and cell cycle distribution</td>
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<td>HEK-293T, HCT8, HCT116, HT29, LoVo, and SW480</td>
<td>(i) Induced 5-FU resistance (ii) Inhibition of miR-204-5p and upregulated its target genes (e.g., bcl2, mib22a, and creb1)</td>
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<td>(i) Overexpressed lncRNA UCA1 in CRC tissues and cell lines (ii) LncRNA UCA1 repressed miR-28-5p level, which subsequently increased HOXB3 axis (iii) LncRNA UCA1 elevated MMP2 and MMP9</td>
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<td>(i) Overexpressed lncRNA UCA1 in CRC cell lines (ii) LncRNA UCA1 elevated the expression of MAPK14 to activate MAPKAPK2/HSP27 signaling pathway (iii) LncRNA UCA1/mTOR axis repressed p27 and miR-143 and significantly elevated cyclin D1 and KRAS expression</td>
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<td>(i) CAFs induced lncRNA UCA1 to increase the expression of mTOR (ii) LncRNA UCA1/mTOR axis repressed p27 and miR-143 and significantly elevated cyclin D1 and KRAS expression (iii) LncRNA UCA1 significantly expressed higher in CRC tissue after chemoradiotherapy (iv) Downregulation of LncRNA UCA1 enhanced radiotherapy sensitivity</td>
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<td>Tissue from 32 CRC patients collected immediately after surgical resection</td>
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<td>(i) LncRNA UCA1 inhibited EMT by reducing MMP2, MMP9, ZEB1, and vimentin (ii) 5-fluorouracil resistance of CRC was associated with lncRNA UCA1 abundance that promoted autophagy and inhibited apoptosis (iii) LncRNA UCA1 sponged miR-23b-3p and consequently elevated ZNF281 expression</td>
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<td>25 CRC patients with 5-fluorouracil resistance and 25 CRC patients with 5-fluorouracil sensitivity</td>
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<td>53 CRC patients treated with cetuximab</td>
<td>Caco2-CR and Caco2-CS</td>
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<td>[76]</td>
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that the lncRNA UCA1 may facilitate GC development, progression, and chemoresistance via the interaction with different molecules, signaling pathways, and/or miRNAs.

3.3. Hepatobiliary Cancer. Hepatobiliary cancer comprises tumors present in the liver, gallbladder, and bile duct (cholangiocarcinoma). For instance, Wang et al. showed that
lncRNA UCA1 was highly expressed in HCC and positively correlated with postoperative survival and tumor, node, and metastasis (TNM) stage [78]. In addition, the result also showed that lncRNA UCA1 regulated fibroblast growth factor receptor 1 (FGFR1)/ERK signaling pathway through sponging miR-216b that led to downregulation of the miRNA levels of miR-216b. In contrast, upregulation was detected for fgfr1 gene to activate the ERK signaling pathway [78].

One of the known risk factors for HCC is hepatitis virus infection [79]. Interestingly, hepatitis B virus (HBV) can induce lncRNA UCA1 in HCC cells via their produced X protein (HBx) [55]. LncRNA UCA1 also significantly reduced p27kip1 expression along with the increased expression of EZH2 via histone methylation on p27kip1 promoter region [55]. In addition, ectopically expressed lncRNA UCA1 induced the expression of cyclin-dependent kinase-2 (CDK2) but not for CDK4 and CDK6 where CDK2 regulated cell cycle and apoptosis, and its activity was regulated by CDK inhibitors (e.g., p21 and p27) [55]. However, only p27 expression was suppressed in overexpressed HBx and lncRNA UCA1 HCC cells [55]. Therefore, this finding suggested that the regulating effects of lncRNA UCA1 are protein-specific despite originating from the same upstream mediators.

Apart from lncRNA UCA1, TGF-β1 and HXX2 were also found to be overexpressed in HCC patients [56]. Hu et al. suggested that TGF-β1 promoted HCC cell growth through the induction of energy metabolism and subsequently promoted lncRNA UCA1 expression and its downstream regulator HXX2, an enzyme involved in glycolysis [56]. Most studies have reported that lncRNA UCA1 is prone to regulate miRNA expression, but Zhao et al. revealed that miR-124, a tumor suppressor miRNA, reduced rho-associated protein kinase 1 (ROCK1) to suppress lncRNA UCA1 expression, leading to the inhibition of HCC cell proliferation, migration, and invasion [57]. They further discovered that the expression of both lncRNA UCA1 and miR-124 was not affected by HBV and HCV infections [57]. This finding, however, could be correct if lncRNA UCA1 is the downstream target protein of miR-124 or incorrect if miRNA and lncRNA UCA1 are negatively regulated in which miRNAs usually downregulated when lncRNA UCA1 is overexpressed as in most cancer types reported.

Furthermore, staphylococcal nuclease and tudor domain containing 1 (SND1) can induce the expression of lncRNA UCA1 through its interaction with myeloblastosis proto-oncogene (MYB), a transcriptional activator, by forming SND1-MYB complex [58]. Meanwhile, SND1 itself acts as an antiapoptotic factor in HCC [58]. Again, this finding supported the previous hypothesis that lncRNA UCA1 expression can be induced by another gene or protein.

Meanwhile, an in vitro study involving HCC cells showed that lncRNA UCA1 was substantially induced by arsenic (As) at 10 μM/L with > 4-fold increase, denoting a protective role against As-induced cell death [59]. By using RNA-Seq assay, oxidative stress induced growth inhibitor 1 (OSGIN1) was uncovered to be the most responsive downstream target of lncRNA UCA1, and miR-184 acted as an intermediate for the regulation of lncRNA UCA1 on OSGIN1 expression through ceRNA mechanism [59]. The lncRNA UCA1/OSGIN1 signaling contributed to As-induced autophagic flux blockage through activating mTOR/ribosomal protein S6 kinase beta-1 (p70S6K) cascade and therefore resulting in compromised cell death [59]. Nonetheless, this finding did not directly conclude the relationship of lncRNA UCA1 with HCC progression. However, the arsenic stress might resemble anticytotoxicity effects as arsenic induces cell death. Therefore, future studies should be conducted in order to relate the effects of lncRNA UCA1/OSGIN1/mTOR/p70S6K with HCC progression.

On the other hand, overexpressed lncRNA UCA1 in cholangiocarcinoma (CCA) showed that it could act as an independent prognostic factor in CCA patients [60]. Similar to the finding reported by Wang et al. in GC, Xu et al. also found that enhanced CCA cell proliferation was via the activation of AKT/GSK-3β axis that led to upregulation of cyclin D1 (CCND1) expression [50, 60]. The apoptosis inhibition in highly lncRNA UCA1-expressed CCA cells might be partly due to B-cell lymphoma 2 (Bcl-2)/caspase-3 pathway [60].

LncRNA UCA1 has also been reported to play an important role in CCA metastasis through regulating miR-122/chloride intracellular channel 1 (CLIC1). For instance, both lncRNA UCA1 and CLIC1 were elevated, while miR-122 was reduced in bile duct carcinoma [61]. Also, both lncRNA UCA1 and CLIC1 promoted the phosphorylation of ERK and mitogen-activated protein kinase (MAPK), activating ERK/MAPK signaling pathway to promote cancer cell metastasis [61].

Apart from HCC and CCA, lncRNA UCA1 is also overexpressed in gallbladder cancer (GBC) [62]. The overexpressed lncRNA UCA1 regulated tumor progression through the recruitment of EZH2 to the promoter of both tumor suppressor p21 and E-cadherin that resulted in their suppressed expression [62]. This observation is opposed to what discovered in HCC by Hu et al. for p21, which could be probably explained by different cancer types used.

In short, these findings revealed the association of lncRNA UCA1 in tumor progression, invasion, and metastasis of hepatobiliary cancer by regulating downstream molecules or be regulated by upstream mediators.

3.4. Pancreatic Cancer. Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths worldwide [80, 81]. According to Chen et al., lncRNA UCA1 overexpression was detected in the tissues of 128 pancreatic cancer patients compared to adjacent nontumor tissues [63]. Moreover, lncRNA UCA1 silencing inhibited cell proliferation and induced apoptosis and cell cycle arrest in PC cells [63]. They also found the possible association of lncRNA UCA1 with the inhibition of p27 in their previous study on PC [63]. In addition, lncRNA UCA1 was shown to regulate growth and metastasis by sponging miR-135a in PC [64]. Apart from the interaction with miR-135a, lncRNA UCA1 also inhibited miR-96, a tumor suppressor miRNA, resulting in the upregulation of forhead box O-3 (FOXO3) to promote tumor progression [65].

In PC cells, lncRNA UCA1 demonstrated to promote cell migration and invasion through Hippo pathway by
interacting with key proteins, such as Mps one binder kinase activator (MOB1), large tumor suppressor kinase 1 (Lats1), phosphorylated-Lats1, and Yes-associated protein (YAP) [66]. LncRNA UCA1 bound to MOB1, Lats1, and YAP to form three shielding composites, retaining YAP activation and leading to YAP translocation into the nucleus to induce gene expression for cell proliferation and apoptosis and for LncRNA UCA1 expression itself [66]. Moreover, LncRNA UCA1 also interacted with MOB1, Lats1, and YAP to form ribonucleoprotein complex that could be another reason in regulating gene expression. In addition, upregulation of MMP (e.g., MMP14, MMP2, and MMP9) proteins were also detected in LncRNA UCA1-overexpressed PC cells, suggesting the role of LncRNA UCA1 in invasion and migration [66]. This study indicated that LncRNA UCA1 could interact with key proteins and protein complexes by binding to their promoter region to enhance PC cell progression.

In pancreatic ductal adenocarcinoma (PDAC), LncRNA UCA1 regulated miR-590-3p to increase the expression of oncogenic Kirsten rat sarcoma viral oncogene homolog (KRAS) protein, and KRAS itself can promote LncRNA UCA1 expression [67]. This discovery showed that LncRNA UCA1 and its downstream protein could regulate each other. Previously, Gu et al. reported that LncRNA UCA1 was associated with miR-590-3p in GC cells via the target gene of phosphorylated-Lats1, and Yes-associated protein (YAP) interacting with key proteins, such as Mps one binder kinase kinase (Mps1b) kinase [66]. LncRNA UCA1 bound to MOB1, Lats1, and YAP to form ribonucleoprotein complex that could be another reason in regulating gene expression. In addition, upregulation of MMP (e.g., MMP14, MMP2, and MMP9) proteins were also detected in LncRNA UCA1-overexpressed PC cells, suggesting the role of LncRNA UCA1 in invasion and migration [66]. This study indicated that LncRNA UCA1 could interact with key proteins and protein complexes by binding to their promoter region to enhance PC cell progression.

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can alter the expression of IncRNA UCA1 and enhance resistance to cetuximab in CRC cells in view of the fact that IncRNA UCA1 can transmit cetuximab resistance to sensitive cells [76]. Given this circumstance, exosomal IncRNA UCA1 indeed has a great potential to be used as an evaluation factor for predicting cetuximab chemoresistance in CRC patients.

In summary, IncRNA UCA1 participated significantly in the CRC progression, invasion, migration, metastasis, radioresistance, and chemoresistance. Therefore, IncRNA UCA1 can be a promising molecular target to combat CRC in chemotherapy, as well as in diagnostic and prognostic purpose of CRC patients.

4. Conclusion

This review has provided an insight into the regulatory roles and patterns of IncRNA UCA1 in GI cancer progression and chemoresistance, as well as its underlying mechanisms and interaction with key molecules involved, which may serve as a novel and highly potential molecular target for GI cancer therapy. It has discovered that multiple preclinical and clinical studies supporting the oncogenic role of IncRNA UCA1 in GI cancer. In addition, the potential of IncRNA UCA1 to be used as a prognostic marker has also been reported in several studies, where its expression correlates with the TNM stage of GI cancer [85]. Based on the findings in this review, it was revealed that basic overexpression of IncRNA UCA1 has a positive implication in initiation, proliferation, invasion, migration, and chemoresistance of GI cancer, although contradictory findings claim that it also has anticancer activity, via the interactions with upstream and/or downstream molecules, signaling pathways, or biological processes. The regulatory roles of IncRNA UCA1 in GI cancer progression are relatively observed more in GC followed by CRC. Comparatively, the regulation of chemoresistance by IncRNA UCA1 has so far discovered only in GC and CRC [16]. In general, IncRNA UCA1 interacts with miRNAs, leading to the reduction of its target gene expression, such as sponging miR-185-5p, in CRC. Moreover, a similar miRNA sponging activity by IncRNA UCA1 can be observed in different GI cancers, such as miR-590-3p in GC and PDAC [46, 67]. IncRNA UCA1 also modulates several gene expressions through epigenetic regulation, particularly associated with histone and chromatin modifications. For instance, IncRNA UCA1 interacts with EZH2 to induce histone methylation as observed in GC, HCC, and CCA [50, 55, 62].

The strategy of IncRNA UCA1 silencing conducted by many researchers showed a promising result in combating GI cancer progression and chemoresistance. Moreover, targeted therapies against IncRNA UCA1 can also be developed for cancer therapy. The approaches that could be taken to achieve this purpose include IncRNA UCA1 silencing via RNA interference (RNAi) and structural disruption of IncRNA [86, 87]. In addition, the research of active compounds from the natural products, particularly plants, also could be considered in order to achieve this purpose. This is because the active phytochemicals in many herbal plants have shown to exert potent cytotoxic effects against various cancers, including GI cancer [88–90]. In conclusion, IncRNA UCA1 has been identified as a novel and potential molecular target for GI cancer in the last decade based on its potent regulatory roles in cancer progression and chemoresistance. However, to enhance its translation possibility to clinical trials, more preclinical studies using both in vitro and in vivo models should be conducted to further explore the key mechanism of actions underlying its regulatory roles. Also, IncRNA UCA1, particularly enriched in exosomes, can be a potential diagnostic and prognostic biomarker compared to other molecular targets due to its high stability and availability in various human body fluids, including urine for BC [13], serum for HCC [91], and plasma sample in early GC [42], as well as its possible simplicity of extraction and diagnostic testing procedures.

Data Availability

The data supporting this manuscript are extracted from the previously reported studies and data sets, which have all been cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

All authors contributed equally to this paper.

Acknowledgments

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