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REVIEW ARTICLE

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Role of *Helicobacter pylori* infection in the manifestation of old age-related diseases

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Abstract

Helicobacter pylori is one of the most prevalent infection worldwide. It affects individuals of different age groups. Elderly people tend to resist eradication treatment and worsening of infection can lead to several gastric and non-gastric pathologies. Aging-associated cellular and molecular alteration can increase the risk of other pathologies such as osteoporosis, Alzheimer's disease, Parkinson's disease, respiratory and renal dysfunction, and cancer in geriatric patients, more than other age groups. This review article highlights some of the most common old age diseases and the role of *H. pylori* infection as a risk factor to worsen the conditions, presented by the molecular evidences of these associations. These studies can help clinicians to understand the underlying pathogenesis of the disease and identify high-risk patients, aiding clearer diagnosis and treatment.

KEYWORDS

aging-associated disease, elderly population, *Helicobacter pylori*

1 | INTRODUCTION

Aging is one of the inevitably dominant risk associated with many diseases.

Several biological factors contribute to this etiology which include loss of telomeres, stem cells activity and metabolism, escalation of environmental and biological stress, dysfunctioning of various micro- and macromolecules, and cell cycle and weakening of immune system (Franceschi et al., 2018). In case of cellular and molecular damage before elderly age, injury is healed to maintain the hemostasis. Nonetheless, with aging, repair mechanism is slowed or completely halted, leading to number of pathologies (Cortopassi, Gurung, & Pinto-Plata, 2017).

Nearly half of the world's population is infected by *Helicobacter pylori*; however, its prevalence varies geographically (Melese, Genet, Zeleke, & Andualem, 2019).

Cytotoxin-associated gene A (CagA) and vacuolating cytotoxin (VacA) antigens are chiefly responsible for the pathogenesis of *H. pylori* infection. Lipopolysaccharides, flagellin, and other toxins have strong ability to manipulate host immune response by the activation of chemokine and cytokine production pathways, recruitment of immune cells, production of autoantibodies, and having a long-term chronic systemic inflammatory response (Chmiela & Gonciarz, 2017).

With age, *H. pylori* infection is seen to bring about gastric changes such as increase in pepsinogen II and gastrin-17, and subsequent decline in pepsinogen I:II ratio, which might manifest other pathologies (Morandini et al., 2018; Shan, Bai, Han, Yuan, & Sun, 2017). *H. pylori*-infected patients remain asymptomatic in a greater portion of their lives, whereas greatest zone of gastric problems is consequently associated with *H. pylori* infection such as peptic ulcers,

mucosa-associated lymphoid tissue lymphoma, functional dyspepsia, and gastric cancer. Additionally, it is also associated with the risk of extragastric diseases (Zendehdel & Roham, 2019). In geriatric patients, 70% of the infection is seen in the form of gastric diseases, with higher severity and hospitalization rate.

Treatment of *H. pylori* infection is based on triple therapy that includes: clarithromycin, metronidazole, and a proton pump inhibitor (PPI). Failure to respond to this treatment is likely due to the development of resistance against antibiotics, particularly in geriatric population (Moradniani et al., 2018). Elderly patients, who are already on drugs, also fail to respond to this treatment, caused by alteration in the interaction of the drugs such as omeprazole (PPI) with cardiovascular medicines (Cizginer, Ordulu, & Kadayifci, 2014). Recent studies have shown that elderly patients are 2–3 times more prone to antibiotic resistance against 100s of strains of *H. pylori* (Boyanova et al., 2017; Shavakhi et al., 2007). In a recent study, Kobayashi et al. (2019) demonstrated that super-elderly patients (aged > 75 years) are more prone to acquire *H. pylori*-associated gastric and duodenal ulcers; nonetheless, the eradication efficacy did not vary in comparison to the other age groups.

The main aim of this review is to highlight extragastric risk factor associated with *H. pylori* infection in geriatric patients (summarized in Figure 1) and the corresponding mechanisms that associated *H. pylori* infection with the diseases.

2 | MUSCULOSKELETAL DISORDERS

Numerous orthopedic diseases are concerned with aging such as osteoarthritis, osteopenia, and sarcopenia. Degeneration of tissues, ligaments and cartilage, loss of strength, frailty, obesity, infection, and several deficiencies can be the cause of these pathologies.

2.1 | Osteoporosis

Reduction in bone mineral density (BMD) and bone quality are two main etiologies of osteoporosis. Most of these cases are mediated by aging due to loss of equilibrium between bone formation and bone loss, mediated by osteoblasts and osteoclasts, respectively. The imbalance of osteoprotegerin and receptor activator of nuclear factor-κ kappa B ligand (OPG/RANKL) pathway plays a significant role in pathogenesis of the disease (Song, Xie, Peng, Yu, & Peng, 2015).

Studies have shown that *H. pylori* infection can lead to osteoporosis due to age-related decline in BMD and systemic inflammation caused by the infection (Heidari, 2015; Pan, Huang, Chuah, Chiang, & Loke, 2018). Nonetheless, contradictory reports are also seen in this regard (Abdolahi, Aghaei, & Naghdi, 2017; Upala, Sanguankeo, Wijarnpreecha, & Jaruvongvanich, 2016). Kim et al. (2014) reported that atrophic gastritis can increase the risk of osteoporosis by 1.89-fold in elderly population.

H. pylori infection, leading to metabolic abnormalities, is also associated with the onset of osteoporosis in aged people (Lu, Hao, Liu, Li, & Wang, 2018). Furthermore, treatment with PPI, such as pantoprazole, can also exacerbate loss of bone density and growth, marked with decrease in levels of calcium and osteocalcin concentrations (Matuszewska et al., 2016). However, early eradication therapy for *H. pylori* infection is likely to reduce the odds of developing osteoporosis (Shih et al., 2016). *H. pylori* can also cause severe decline in serum vitamin D levels, hence compromising bone health (Mut Surmeli et al., 2018) and leading to metabolic syndrome (discussed later) (Chen et al., 2016a; Zendehdel & Arefi, 2019).

2.2 | Osteoarthritis (OA)

It is a chronic condition associated with the progressive loss of functionality of bones and associated joints. In geriatric population, loss of cell function, increased oxidative stress, chronic inflammation, and genetic changes can lead to the onset of OA (Loeser & Lotz, 2016).

Different mechanisms have been proposed to understand the pathology of the disease. Studies have shown that decrease in the expression of tissue growth factor-β (TGF-β), upregulation of matrix metalloproteinase (MMP), age-related alteration in the methylation of DNA, and elevated chronic inflammation and related cytokines such as TNF-α, IL-1β, IL-6, IL-8 are some of the causes of OA (Chen, Shen, et al., 2017).

Studies have shown that *H. pylori*-related upper gastrointestinal bleeding is common in aged patients with OA (Kim et al., 2016). To it, the usage of drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and PPI in patients with OA might worsen this effect (Chan et al., 2010; Rogoveanu, Streba, Vere, Petrescu, & Traistaru, 2015).

2.3 | Sarcopenia

Sarcopenia is characterized by the age-related reduced skeletal muscle mass and associated activity, as seen in elderly patients. It leads to physical and systemic disabilities. Exercise and hormone-based treatment, such as testosterone, insulin-like growth factor-1 (Dhillon & Hasni, 2017), and ghrelin, have been used to increase the muscle mass. Ghrelin is found to play a significant role in muscle mass and boosting of physical activity (Tamaki et al., 2017). Baeg et al. (2015) demonstrated that elderly women who are *H. pylori* positive,

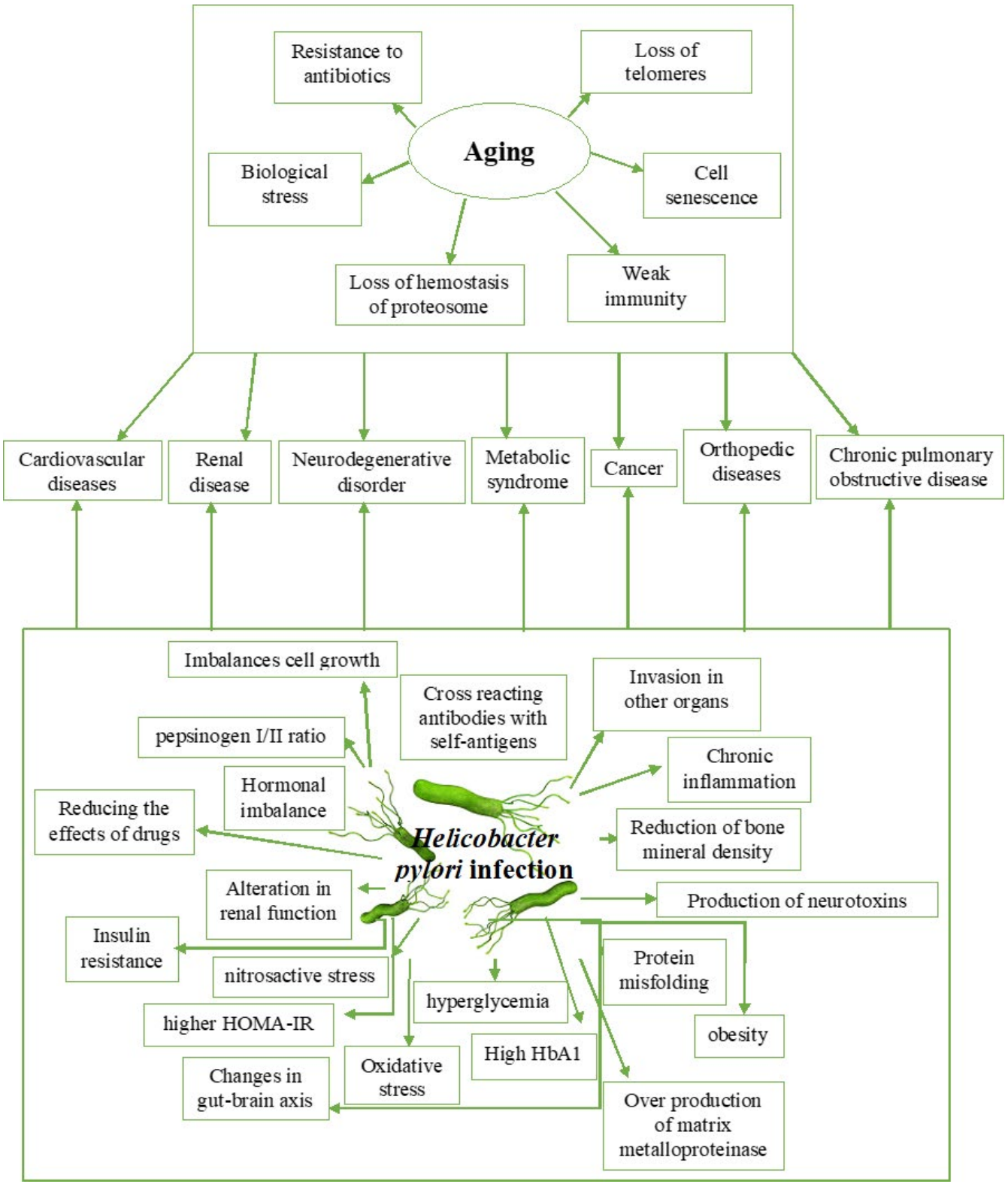

FIGURE 1 summarizes the links between aging, *Helicobacter pylori* infection, and extragastric diseases

as compared to the ones who took *H. pylori* eradication treatment, had lower muscle mass. These results were parallel with the prevalence of sarcopenia-associated risk factors obesity, diabetes, increased WBC count and metabolic syndrome. The study by Mantero et al. (2018) also predicted that eradication of *H. pylori* normalizes the levels of ghrelin, thereby suggesting that it might play a significant role in restoring muscle mass.

Furthermore, the vast amount of studies has proven that *H. pylori* infection leads to impairment of systemic immunity. It

also leads to chronic inflammation by activation of various pathways and expression of microRNAs for the production of inflammatory cytokines (IL-1β, INF-γ, IL-6, and TNF-α). Macrophages (M1) and neutrophil-mediated inflammation is also elevated due to the infection (Cadamuro, Rossi, Maniezzo, & Silva, 2014). Once these macrophages and neutrophil migrate to the skeletal muscle, they can lead to inflammation in the muscles and injury. Progression of the age if seen in the form of chronic systemic inflammation, can cause loss of muscle mass by the breakdown of muscle protein (Franceschi et al., 2018).

3 | CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease is defined by the obstruction in the airflow to the lungs to due chronic inflammation due to presence of harmful particles (e.g., cigarette smoke). It is widely associated with several other morbidities and is highly prevalent in geriatric population (Azargoon, Gholami, Farhadi, Chegni, & Zendedel, 2016). Changes in the recoiling capacity of the lungs, lead to difficult expiration with the aging. Underlying causes such as loss of physical activity, history of smoking, and exposure of harmful gases adds to pathophysiology of the disease (Cortopassi et al., 2017).

H. pylori infection is strongly characterized as one of the risk factors for the development of COPD in elderly patients; CagA and IgG seropositivity are seen in these patients (Samareh Fekri, Hashemi Bajgani, Rasti, Yazdani, & Mollaie, 2014; Wang, Liu, Zhang, & Lei, 2015). Peng et al. (2017) and Wang, Guan, et al. (2015) reported that odds ratio of *H. pylori* infection in COPD patients is 2.11. *H. pylori* pathogens and DNA have been seen in the lungs and oral cavity of the infected individuals, thereby it is likely to initiate inflammatory response in the lungs. Expression of receptors like Toll-like receptors 2 and 4 (TLR-2 and TLR-4) and advanced glycation end-products (RAGE) in the pulmonary epithelium is responsible for the recognition of *H. pylori*. Long-term exposure to these pathogens, leads to chronic inflammatory response and oxidative stress-like conditions (Zendedel et al., 2015). The presence of other harmful particles in the lungs can significantly enhance the immune response, initiated by the bacterial invasion (GonzÁlez, Araya, & Rojas, 2018).

4 | RENAL ABNORMALITIES

Similar to other tissues, upon aging, functions of renal tissue are largely compromised too. The decrease in glomeruli filtration rate, alterations in the permeability, reabsorption and urine concentration, lessening of podocytes, nephrons and kidney volume, nephrosclerosis, hypertrophy, and cyst formation are some of the normal renal changes associated with healthy aging (Denic, Glassock, & Rule, 2016).

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are the most significant age-related renal diseases, reported in elderly patients (Portilla Franco, Tornero Molina, & Gil Gregorio, 2016; Poveda et al., 2017). Eradication of *H. pylori* is likely to have a protective effect against CKD (hazard ratio: 0.69) (Wang et al., 2016a).

Studies have shown that in geriatric patients, co-existence of peptic ulcer and CKD is higher than other age groups (Liang et al., 2014) To it, its severity can advance to renal transplant stage (Hussein et al., 2016). Similarly, infected patients above 75 + years are also more prone to develop ESRD, compared to other ages. These patients are mostly hypertensive and diabetic, thereby increasing the risk of ESRD. Cardiovascular disorders are also common in *H. pylori*-infected individuals; hence this could connect the two pathologies. Furthermore, systemic inflammation, as a result of *H. pylori* infection marked by elevated levels of C-reactive protein (CRP), TNF-α, and IL-6, are also associated with the loss-of-kidney function. *H. pylori* can lead to several alterations in the renal function that can be seen as, proteinuria, microalbuminuria and other metabolic products. It also increases levels of homocysteine and asymmetric dimethylarginine, markers of CKD, in serum (Lin et al., 2015). *H pylori*-mediated decrease in pepsinogen I/II ratio is characterized by the diabetes-associated nephropathy (Senmaru et al., 2013). Eradication therapy of *H. pylori* infection can decrease the risk of CKD (Wang et al., 2016a).

5 | METABOLIC SYNDROME

Metabolic syndrome is a cluster of several disorders comprising abnormality in the lipid profile, insulin resistance, visceral obesity, hypertension, increased levels of white blood cells (Li et al., 2016), and hyperglycemia. These factors can lead to several cardiovascular disorders and diabetes mellitus. It is a common condition affecting geriatric population (Kapil et al., 2018; Kapil et al., 2018), also leading to frailty (Lopez-Garcia et al., 2017), sarcopenia (Chang et al., 2015), increasing the risk of fracture (Chen, Chen, Hsieh, Kuo, & Chien, 2017), osteoporosis (Cui et al., 2016), and affecting cognitive and functional abilities in this group of population (Viscogliosi, Donfrancesco, Palmieri, & Giampaoli, 2017). Yang and Xuan (2016) demonstrated that *H. pylori* infection is associated with the increased risk of metabolic syndrome in Chinese population with the odds ratio of 5.427.

Helicobacter pylori infection in geriatrics can increase the risk for the development of insulin resistance (Chen et al.,

2015), hyperglycemia, and increased body mass index (BMI) (Yang, Xuan, & practice, 2016; Zhang et al., 2015). Together *H. pylori* infection and vitamin D deficiency can increase the risk of developing metabolic syndrome up to twofold (Chen et al., 2016a). Additionally, eradication of *H. pylori* can restore the levels of adiponectin, a marker of obesity in metabolic syndrome (Ando et al., 2013).

6 | CARDIOVASCULAR DISEASES (CVD)

Aging in cardiac tissue is seen in the formation of decline in contractility of the myocardium, ejection fraction, and elevation in the arterial stiffness. These phenomena are validated in different studies. Vendrov et al. (2015) demonstrated that NAPDH-mediated oxidative stress corresponds to aging-related incidence of CVD. Increased concentration of mitochondrial reactive oxygen species leads to aortic stiffness and atherosclerosis. In a recent article, cellular senescence with the progression of the age is seen to be related with CVD. This is due to elevated systemic inflammatory response and oxidative stress. Senescence of endothelium is seen to result in heart failure with persevered ejection fraction that is also commonly seen in geriatric population (Shakeri, Lemmens, Gevaert, Meyer, & Segers, 2018). It is seen that *H. pylori*-seropositive patients have high levels of low-density lipoproteins and eradication of *H. pylori* infection can lower these levels (Nam, Ryu, Park, & Park, 2015. To it, *H. pylori*-positive geriatric patients have increased risk of developing atherosclerosis and acute coronary syndrome (Carvalho et al., 2018; Lai, Yang, Lin, & Kao, 2015). They are also at the risk of acquiring myocardial infraction, stroke, and peripheral artery disease (Rahmani et al., 2017; Vijayvergiya & Vadivelu, 2015).

Aging and *H. pylori* infection is associated with changes in gastric chemicals and progression of cardiovascular diseases (Mladenova, 2019; Shan et al., 2017). *H. pylori* infection is seen to result in hypertension, increased arterial stiffness, and lipid profile. Atherosclerosis is one of the outcomes of chronic inflammation via different pathways. Patients with *H. pylori* infection are found with increased endothelial dysfunction due to high levels of CRPs, and vascular and intracellular adhesion molecules that mediate inflammation. To it, other inflammatory markers like TNF-α, IL-1β, IL-6, IL-8, INF-γ (interferon gamma), and several coagulation factors are also elevated in such conditions that lead to vasoconstriction, impaired endothelial function, that is also mediated by the levels of homocysteine, overproliferation of skeletal muscle cells, and production of matrix metalloproteinase, leading to atherosclerosis and acute coronary syndrome, respectively. These inflammatory chemicals are upregulated by *H. pylori* infection via cyclooxygenase enzyme-2, toll-like receptors, and activation of mitogen activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), and other such pathways (Vijayvergiya & Vadivelu, 2015). Furthermore, cross-reacting antibodies of *H. pylori*, such as anti-urease and anti-heat shock protein (anti-Hsp) antibodies, can bind to antigens of endothelium, skeletal muscle cells, and cardiomyocytes, thereby maintaining plaques formation and directing immune-destruction of the tissue (Chmiela & Gonciarz, 2017).

In recent studies, it is found that *H. pylori* and associated morbidities are likely to increase the risk of atherosclerosis (Hu et al., 2017; Yu et al., 2019).

6.1 | Diabetes mellitus (DM)

Ample studies have reported evidence-based report regarding the positive association between diabetes mellitus and *H. pylori* infection (Hosseininasab Nodoushan & Nabavi, 2019), particularly in aged individuals (Dat, Yip, & Hanegbi, 2016). Besides, diabetes-related complications such as diabetic nephropathy (Bajaj et al., 2014) and neuropathy (Wang, Fu, & Lv, 2014), diabetic gastroparesis (Huang, 2017), and retinopathy (Agrawal et al., 2010) also validate the association between diabetes mellitus and *H. pylori* infection. Li et al. (2017) in a meta-analysis reported that *H. pylori* infection is chiefly greater in diabetes mellitus patients than in non-diabetes mellitus individuals (odds ratio: 1.69).

H. pylori-positive individuals have higher HOMA-IR (homeostatic model assessment-insulin resistance) levels and corresponding oxidative stress (Vijayvergiya & Vadivelu, 2015). Subsequently, HbA1 (glycated hemoglobin) and 8-hydroxydeoxy guanosine (8-OHdG), damage to guanine in DNA due to oxidative and nitrosactive stress (Flint, Stintzi, & Saraiva, 2016) as a result of infiltration of neutrophil, are also elevated parameters in infected diabetic patients (Nasif, Mukhtar, Nour Eldein, & Ashgar, 2016).

Likewise, the control of diabetes by the usage of glucophage can also lead to lower risk of developing *H. pylori* infection (Tseng, 2018). Treatment of *H. pylori* might be affected by the imbalance in glucose levels (Nam et al., 2019). In elderly patients, hyperglycemic conditions with *H. pylori* infection can also lead to colorectal cancer and arterial plaques (Hu et al., 2017).

7 | NEUROLOGICAL DISORDER

Dementia (vascular dementia [VD] and Parkinson's disease [PD]) and Alzheimer's disease (AD) are the most common types of neurological disorders associated with the progression of age (Callixte et al., 2015). These are characterized by the loss of memory (dementia), difficulty to perform cognitive and physical function, and follow orientation. Both,

AD and PD, are characterized by the deposits of misfolded protein like β-amyloid and α-synuclein, respectively. These neurobiological markers and scans are performed to detect the disease.

Pathogenesis of AD as seen from different aspects include aging of brain, oxidative stress, impairment of mitochondrial function, neuroflammation (involving brain cells and other immune cells), and corresponding increased levels of serum TNF-α, IL-1β, IL-6, INFγ, and tissue growth factor-β (TGF-β). IL-6 is permeable to blood–brain barrier (BBB), and IL-1β and TNF-α mediate changes in β-amyloid protein (ligand for formyl peptide receptor [FPR]) and alter synapses. Similarly, oxidative stress leads to increased levels of oxidized protein and lipid products and cause cell senescence, which are also identified in AD. Variations in the input from the gut can also impose their effects via gut–brain axis. These can include degenerative signals from the bacterial toxins and thereby studies have also found association of AD with different infectious agents (Caputi & Giron, 2018; Franceschi et al., 2018). *H. pylori* is found to alter the gut–brain axis such that it can lead to neurological disorders like depression, anxiety, dementia, schizophrenia, and neurodegenerative pathologies (Budzyński & Kłopocka, 2014). Animal-based study has shown that *H. pylori* infection upregulates the expression of various classes of FPRs and other genes, significant for the AD, by Hp (2–20) peptide of the bacteria. These genes have neuroprotective (MTRNR2L2, APOE) and anti-inflammatory (ANXA1) roles (Contaldi et al., 2017). Other evidences suggest that *H. pylori* can enter brain via oral–nasal passage and *H. pylori*-infected monocytes, able to bypass the process of autophagy, can cross BBB, and lead to inflammation (Doulberis et al., 2018). Moreover, *H. pylori* can also cause misfolding of tau protein, one of the misfolded proteins responsible for AD (Wang, Zeng, et al., 2015).

A systemic review of 260 studies concluded that *H. pylori* is likely to induce risk of dementia. Most of these studies were conducted on patients with the age of 60-years and above (Shindler-Itskovitch, Ravona-Springer, Leibovitz, & Muhsen, 2016). This is likely because of the chronic inflammation in both the diseases, cross-linking each other (Xu, Wang, Liu, Cui, & Zhao, 2016). Consequently, elevated levels of serum YKL-40 (also known as chitinase-3-like protein 1 [CHI3L1]) are a significant marker for many inflammatory diseases, including neurodegenerative ones, such as Alzheimer's (Muszyński, Groblewska, Kulczyńska-Przybik, Kułakowska, & Mroczko, 2017). Xu, Wang, Liu, Cui, Lu, et al. (2016) demonstrated that CHI3L1 is upregulated in *H. pylori*-positive individuals, presenting vascular dementia and hyperlipidemia in aged individuals.

Bu et al. (2015) in their study showed that onset of Alzheimer's disease in elderly patients, as seen by the increased levels of β-amyloid, is associated with exposure to infectious microbes, including *H. pylori.*

H. pylori infection is also associated with the increased risk of PD in geriatric individuals (Dardiotis et al., 2018). Augustin et al. (2019) reported that PD patients presenting *H. pylori* infection have 12 times increased rate of mortality. There are several different hypotheses to justify these studies. The levels of neurotoxins like cholesterol glucosides and methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are increased as a result of chronic infection that can deteriorate brain functionality. Accumulation of α-synuclein in the nerve endings of the gut due to infection correspondingly contributes to the pathology of PD (Ito et al., 2013). It can also lead to the destruction of neuron by crossing the BBB via nasal passage. Additionally, disruption of the motor function as a result of bacterial invasion can affect the absorption of levodopa drug (for the treatment of PD), where the eradication therapy can alleviate these effects. These motor functions are greatly impaired in elderly patients especially (Çamcı & Oğuz, 2016). Autoantibodies, primarily generated against bacterial antigens can also cross the BBB and trigger the degenerative response. Alterations in BBB, as a result of changes in gut microbiota, has also been suggested as one of the causes of *H. pylori* infection-mediated PD (McGee, Lu, & Disbrow, 2018).

8 | CANCER

Despite cancerous and aging cells being functionally opposite (hyperproliferation vs. cell senescence), there are several other factors that can lead to carcinogenesis in aging cells. These include age-associated genetic and epigenetic alterations, abnormal proliferation of damaged stem cells, loss of protein homeostasis such as that of heat shock proteins, lysosome, decline in autophagy, and nutritional imbalance (Aunan, Cho, & Søreide, 2017). Levi, Sochacki, Khoury, Patel, and Majumdar (2014) showed that *H. pylori* infection cancer stem cells aid progression of neoplasm. This is mediated by the upregulation of the Wnt/β-catenin pathway, increasing the levels of Nanog, Oct4, and c-myc that is also overregulated in carcinogenic conditions (Yong et al., 2016; Zhan, Rindtorff, & Boutros, 2017).

Chronic systemic inflammation, due to long-term colonization of *H. pylori* infection, increases the risk of lung cancer in geriatric population (Samareh-Fekri et al., 2016). Traces of *H. pylori* has been seen in prostate tumors in elderly (Al-Marhoon et al., 2015), which is facilitated by imbalance between apoptosis and growth of the cells (Verit et al., 2015). One of the possible links between the two diseases could be the chronic inflammation and activation of cell proliferating pathways (already discussed) (Dang & Liou, 2018).

The odds ratios of correlation between colorectal cancer/adenoma and *H. pylori* infection have been reported from

1.15 to 10.6 (Butt & Epplein, 2019). Co-existence of insulin resistance, hyperglycemia, and *H. pylori* is associated with the increased risk of colorectal adenoma in aged people (Hu et al., 2017; Hu et al., 2017). VacA virulency is associates *H. pylori* with colorectal cancer (Mut Surmeli et al., 2018), verified in a recent meta-analysis (Zhao, Wang, & Wang, 2016), it increases the risk of colorectal neoplasm and adenocarcinoma (Kim et al., 2017). In such patients, immune tolerance of the bacteria is elevation of tryptophan:kynurenine ratio and its metabolite, neoprotein, that mark the inflammatory response (Christensen et al., 2018; Engin, Karahalil, Karakaya, & Engin, 2015).

H. pylori-seropositive patients are also more prone to acquire laryngeal and hypopharyngeal carcinoma (Guilemany, Langdon, Ballesteros, & Blanch, 2014; Zhou, Zhang, Yang, Zhou, & Tao, 2016).

9 | CONCLUSION

Helicobacter pylori infection can be chronic and bypass various eradication therapies. In elderly patients, antibiotic resistance, chronic inflammation, compromised immunity, and retardation of cell activities are the suggested causes in this regard. Due to long-term colonization of *H. pylori* infection, its effects are seen systematically, leading to several other extragastric disorders. Despite contradictory studies reporting no association between *H. pylori* infection and some extragastric pathologies (Fotouk-Kiai et al., 2015; Yu et al., 2014), aging-associated risk factors should be considered. Future studies relating aging and *H. pylori* infection with extragastric disease can help to provide vivid evidences.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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