Contributing factors common to COVID-19 and gastrointestinal cancer

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Received September 12, 2021; Accepted November 4, 2021

DOI: 10.3892/or.2021.8227

Abstract. The devastating complications of coronavirus disease 2019 (COVID-19) result from the dysfunctional immune response of an individual following the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Multiple toxic stressors and behaviors contribute to underlying immune system dysfunction. SARS-CoV-2 exploits the dysfunctional immune system to trigger a chain of events, ultimately leading to COVID-19. The authors have previously identified a number of contributing factors (CFs) common to myriad chronic diseases. Based on these observations, it was hypothesized that there may be a significant overlap between CFs associated with COVID-19 and gastrointestinal cancer (GIC). Thus, in the present study, a streamlined dot-product approach was used initially to identify potential CFs that affect COVID-19 and GIC directly (i.e., the simultaneous occurrence of CFs and disease in the same article). The nascent character of the COVID-19 core literature (~1-year-old) did not allow sufficient time for the direct effects of numerous CFs on COVID-19 to emerge from laboratory experiments and epidemiological studies. Therefore, a literature-related discovery approach was used to augment the COVID-19 core literature-based 'direct impact' CFs with discovery-based 'indirect impact' CFs [CFs were identified in the non-COVID-19 biomedical literature that had the same biomarker impact pattern (e.g., hyperinflammation, hypercoagulation, hypoxia, etc.) as was shown in the COVID-19 literature]. Approximately 2,250 candidate direct impact CFs in common between GIC and COVID-19 were identified, albeit some being variants of the same concept. As commonality proof of concept, 75 potential CFs that appeared promising were selected, and 63 overlapping COVID-19/GIC potential/candidate CFs were validated with biological plausibility. In total, 42 of the 63 were overlapping direct impact COVID-19/GIC CFs, and the remaining 21 were candidate GIC CFs that overlapped with indirect impact COVID-19 CFs. On the whole, the present study demonstrates that COVID-19 and GIC share a number of common risk/CFs, including behaviors and toxic exposures, that impair immune function. A key component of immune system health is the removal of those factors that contribute to immune system dysfunction in the first place. This requires a paradigm shift from traditional Western medicine, which often focuses on treatment, rather than prevention.

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Key words: coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, gastrointestinal cancer, colon cancer, stomach cancer, esophageal cancer, immune system dysfunction, contributing factors, literature-related discovery

Introduction

Overview. The present study aimed to demonstrate commonality between the contributing factors (CFs) to coronavirus disease 2019 (COVID-19) and gastrointestinal cancer (GIC), and to demonstrate that the bases for these superficially different diseases have important similarities. Much of the underlying motivation for the present study has been previously presented (1,2) and is thus not repeated herein.

The virus associated most closely with COVID-19 [severe acute respiratory syndrome (SARS)-coronavirus 2 (CoV-2)]

is transmissible. The occurrence of serious consequences from this transmission is dependent on the health of the host's immune system (3-5). In the model proposed by the authors, these severe consequences of COVID-19 result from the effective exploitation of a dysfunctional immune system by the SARS-CoV-2 virus. In this exploitive process, genetic disposition and real-life exposures to multiple toxic stressors, as well as toxic behaviors, lay the groundwork for immune system dysfunction. Following SARS-CoV-2 exposure, the dysfunctional immune system is unable to neutralize the SARS-CoV-2 virus, thereby allowing the virus to enter and replicate in cells and trigger a chain of events, ultimately leading to COVID-19 (3,4).

If immune system dysfunction is a/the major factor in the severity of both infectious and chronic diseases, then a necessary, although not necessarily sufficient, condition for prevention and successful longstanding treatment is a reduction of those factors that contribute to immune system dysfunction. The virology-centric approach currently used for COVID-19 reflects damage control for a dysfunctional immune system (e.g., quarantine, face masks, vaccines, anti-viral treatments, etc.). A toxicology-centric approach would be aimed at identifying and removing the CFs to immune system dysfunctionality. Its evidentiary basis would require going beyond current single-stressor laboratory experiments to more comprehensive stressor combination experiments (2,6).

It was hypothesized that the links between CFs to COVID-19 and GIC are similar, based on independent observations of chronic disease CFs and COVID-19 CFs. The present study aimed to examine this hypothesis.

Notable demonstrations of the present study. Myriad techniques were developed/exploited and integrated for the present study, and are explained in detail in the Data and methods section. Multiple findings resulted from this approach, although two major demonstrations stand out.

First was the demonstration that a number of crucial CFs common to GIC and COVID-19 exist. This provides evidence of the unity of diseases (infectious and chronic) heretofore considered and treated as separate entities, and is a step along the pathway to a unified theory of disease.

Second was the demonstration that CFs indirectly related to COVID-19 (the CF did not appear in the COVID-19 core literature, but was located in a literature directly related to COVID-19; e.g., hyperinflammation, hypercoagulation, hypoxia, etc.) exhibited high promise of being validated eventually as directly related to COVID-19 (the CF appeared in in the COVID-19 core literature). Having the ability to identify promising CFs using literature related directly to the target disease literature is the mirror image of having the ability to identify promising treatments for repurposing, and would be of substantial value to researchers, research managers, research sponsors, and venture capitalists. It would also serve as an early warning indicator and allow precautionary preventive steps to be taken for a target disease of interest before a CF had been confirmed as directly related to that disease.

Commonality of CFs to GIC and COVID-19

Background. The first author and colleagues have been developing protocols to prevent and reverse chronic diseases (7,8). The central component of these unique protocols is the identification and elimination of CFs to these chronic diseases. However, the question arises of whether the aforementioned approach for preventing and reversing chronic diseases can be applied successfully for preventing and reversing communicable diseases that exploit immune system dysfunction, such as COVID-19.

COVID-19. Over the past two decades, there have been at least three major coronavirus-based infectious disease outbreaks/epidemics/pandemics: SARS in 2002-2003; Middle East respiratory syndrome (MERS), which commenced in 2012; and COVID-19, which commenced in December, 2019. A comparative analysis of the clinical and laboratory differences and similarities among SARS-CoV, MERS-CoV and SARS-CoV-2 (presented in Table I) highlights two points: i) The most common clinical symptoms (such as fever, cough, myalgia, etc.) that were present have relatively similar extent in patients with MERS and SARS-CoV-2; ii) in synchrony, laboratory findings documented similar alterations of metabolic markers.

The literature data appear to underline various immunological characteristics among SARS-CoV, MERS-CoV and SARS-CoV-2 (9). Given the caveat that the cytokine profile is extremely variable by depending on numerous factors such as the phase of clinical course, disease severity, and types of cytokines analyzed; inter alia, it is of particular interest to mention that the cytokine profile has been found to be practically unaltered in patients with MERS-CoV who developed severe disease (10). Indeed, as previously demonstrated, interferon (IFN)-γ, interleukin (IL)-10, IL-12p70, IL-12/IL-23p40 and IL-17 were not detected in the serum of any patients with MERS-CoV during the course of disease. Only IFN-β, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β3 and IL-1α were detected in a few patients, although they did not exhibit any significant association with the clinical course or the severity of illness (10). Hence, these data may suggest a dominant role of the disrupted cytokine profile, i.e., the so-called cytokine storm, in determining the disease severity that affects the SARS patients (11). Finally, another crucial similarity among them is the demographic affected most severely: The elderly population and others who have comorbidities associated with dysfunctional immune systems (1,3,12-16).

GIC. Nature Research (17) defines the scope of GIC as: 'malignant conditions of the gastrointestinal (GI) tract and other organs involved in digestion, including the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus'. To generate the core GIC literature required for the present study, the MeSH Tree scope (which includes Pubmed MeSH terms only) (18) was selected, and this was augmented with the text equivalents of the myriad cancers listed on the MeSH Tree for GIC. The final GIC query selected for GIC core literature retrieval from Pubmed is presented as supplementary material (Appendix S1).

As regards, incidence and prevalence, GIC is a relatively prevalent cancer. Worldwide, the GIC burden remains high (19). In the USA, colorectal cancer was the fourth leading cause of new cancer diagnoses in 2020 (20). Globally, colorectal cancer also has the fourth highest incidence, with 1.9 million annual diagnoses (19). Stomach cancer was the

Table I. Comparative clinical and laboratory overview of MERS and SARS[a].

Parameter	SARS-CoV (% of patients)	MERS-CoV (% of patients)	SARS-CoV-2 (% of patients)
Clinical characteristics			
Fever	99-100	40-98	65-99
Cough	29-100	18-87	22-82
Myalgia	20-60	7-32	11-44
Shortness of breath	20-60	27-72	4-35
Dyspnea	42-44	5-15	17-40
Chills	15-74	7-87	7-17
Diarrhea	10-50	7-44	1-10
Vomiting or nausea	10-35	7-21	1-13
Chest pain	30	15	2
Headache	15-70	5-13	4-8
Sore throat	11-30	4-1	4-26
Laboratory findings			
Leukopenia $<4x10^9$	7-34	6-14	17-25
Lymphopenia $<1x10^9$	54-75	35	35-70
Thrombocytopenia	20-44.8	17-36	21
Lactate dehydrogenase ↑	71-87	47-49	40-98
Alanine transaminase ↑	23-56	11	17-31
Aspartate transaminase ↑	32-78	15-53	30-37
Mortality rate	3.6-30	60-65	4-28

[a]The information shown in the table has been adapted from a previous study (9). SARS-CoV, severe acute respiratory syndrome coronavirus; MERS Middle East respiratory syndrome. The upward arrows (↑) denote an increase.

5th most common diagnosis, with 1.1 million cases (19). The incidence of esophageal cancer was 604,000 (19).

The risk factors for the development of GIC may be affected by genetic predisposition, geographic location, infection, toxic exposures and other medical conditions or treatments (21-24); however, several risk factors are modifiable, including diet, physical activity, alcohol consumption and smoking (25,26). As obesity has become increasingly prevalent worldwide, increasing associations between obesity and the risk of GICs have been identified (27). There are likely several mechanisms involved, including alterations in endocrine signaling, a relatively high fat and processed meat consumption coupled with a low fiber intake that influences intestinal microbes and immune response, and altered inflammatory cytokines from adipose tissue (27,28).

Toxicology. In its broadest sense, toxicology is the study of the impact that toxic stimuli and toxic behaviors, as well as their combinations, can have on all members of the animal kingdom and their environment. Its two most important components are epidemiological-type studies to identify potential adverse effects of candidate toxic stimuli and behaviors, and laboratory studies to identify mechanisms that link the stimuli to their adverse effects. Toxic stimuli exposures or toxic behaviors can range from acute to chronic, and the doses can span a wide spectrum.

It is well documented that exposure to a wide variety of stimuli, whether they are anthropogenic chemicals (e.g., xenobiotics) or lifestyle-related, etc., is associated with an increased prevalence of chronic diseases. In some cases, the underlying mechanism includes the dysfunction of the immune system. Exposure to particulate matters, fossil fuel derivatives, metals, ultraviolet (UV)-B or ionizing radiation, etc., may contribute to immunodeficiency, which in turn may contribute to the development of chronic diseases. This could critically elevate viral epidemic or even pandemic events and prevalence, such as in the COVID-19 pandemic (3,29), or metabolic disorders (27). A further underlying mechanism may involve metabolic disorders. Chronic inflammation may be promoted by the exposure to stressors during a life course, such as environmental toxicants, processed food (30), infectious agents, overfeeding, or drugs. The improvement of the immune response and inflammatory markers may lead to an improved physiological resilience to disturbances by infectious agents, such as viruses and bacteria, and may possibly lead to milder COVID-19 symptoms.

The robustness of the immune system appears to play a pivotal role. It has even been suggested that it may affect vaccine safety and efficiency (4). Human host autoimmune pathologies may be triggered due to sequence similarities between peptides, introduced by vaccines and human proteins. The protective anti-SARS-CoV-2 antibody immune response may result in a pathogenic autoimmune attack against a genetically predisposed human vaccine recipient. Possible stimuli implicated in the aforementioned mechanism include alcohol consumption, as well as exposure to various toxic metals (31,32).

The functional improvement of the immune system to maintain metabolic homeostasis may be achieved by

administrating specific dietary components, such as fibers and polyphenols, as well as lifestyle changes (e.g., physical exercise), thus maintaining metabolic homeostasis and preventing disease development (33).

Similarly, serum zinc, copper and the metabolism of other biometals, as well as serum metal levels and metal balance and homeostasis, appear to play a crucial role in the mechanisms that affect disease severity by interfering with COVID-19 pathogenesis; these may thus be exploited as COVID-19 severity markers (34).

Relevance to chronic and infectious diseases. In previous studies, authors have demonstrated that the onset and exacerbation of chronic (7) and infectious diseases (3) are greatly affected by toxic modifiable CFs (with genetic factors having different levels of influence). The present study demonstrates that there is strong overlap between the CFs for GIC and COVID-19. Thus, while the outward manifestations (symptoms) of the two diseases appear to differ, some fundamental causes are similar. This may be the reason that the majority of severe consequences of COVID-19 occur in those patients with high comorbidities; the comorbidities and COVID-19 are two sides of the same coin.

Toxicological components constitute the bulk of modifiable CFs responsible for GIC and COVID-19. In both cases, the effects of these toxicological components on the immune system and circulatory system appear to be major contributors to the symptoms and outcomes observed, primarily through increases in inflammation and oxidative stress. Examples of immune system dysfunction center around the hyperinflammation/cytokine storm and severe allergic reactions, while circulatory system dysfunction centers around changes in i) serum properties, such as hypercoagulation; and ii) cardiovascular markers, such as elevated troponin and D-dimer levels. In GIC, the interactions between the immune system and the microbiome (35-38) (Fig. 1) become critical due to the cancer localization in the digestive tract.

Inflammatory factors and coagulation changes exhibit similar clinical manifestations in COVID-19 and GIC. In hospitalized patients with COVID-19, serum IL-6, IL-8, IL-1β and TNF-α levels are an inflammatory cytokine signature linked to coagulopathy and are predictive of COVID-19 severity and associated survival (39,40). Mechanistically, alterations in this inflammatory cytokine signature and the resulting inflammation and tissue injury can function as inducers of increased signaling by thrombin (proteinase-activated) and purinergic receptors, which promote platelet activation and hypercoagulation events, thus determining hypercoagulability (41). In particular, it should be emphasized that increased levels of TNF-α represent a risk determinant for venous thromboembolism (42).

Such a scheme of altered inflammatory factors leading to coagulation disorders appears to be reflected in GIC. In fact, alterations in the levels of IL-8, IL-10 and TNF-α may play crucial roles in the development of gastric cancer (43); TNF-α/TNFR1 signaling promotes gastric tumorigenesis (44); TNF-α gene promoter polymorphisms are linked to a risk of developing venous thromboembolism (45). In essence, alterations in a selected cytokine profile and, in particular, in the levels of TNF-α appear to be a main factor of hyperinflammation and hypercoagulopathy in both COVID-19 and GIC.

The toxicological components included in the present study cover toxic lifestyles (diet, activity, sleep, substance abuse, etc.), medical procedures (drugs, diagnostics, surgery, non-drug therapies, etc.), bio-organisms (fungi, mold, parasites, viruses, bacteria, etc.), environments, occupations, psychosocial events and socioeconomic environments. The laboratory-based evidence for the toxicity of the majority of toxic substances is obtained through single-stressor laboratory experiments, which under-represent real-world effects. The combinations of toxic stimuli reflect real-world exposures, and the doses of substances that can cause damage in combinations are lower than those that can cause damage in single-stressor experiments of those substances. Each of these factors plays a key role in such chronic exposure paradigms, revealing the importance of required further toxic evaluations in order to discover possible routes that would eventually lead to a human risk.

The rapidly growing body of scientific evidence on COVID-19 indicates that in order for a patient to exhibit serious symptoms and side-effects, an underlying dysfunction of the immune system is necessary. Various factors, including genetic predisposition and exposure to toxic stimuli, aid the virus in rendering the immune system vulnerable.

Literature-related discovery and innovation (LRDI). LRDI has been previously described in detail (46-48), and only the essential features relevant to the present study (the discovery component of LRDI: LRD) will be summarized herein. LRD and its subset literature-based discovery (LBD) link two or more disparate literatures to produce discovery. In the medical world, the main application of LRD has been to identify novel treatments for disease (48,49), also known as treatment repurposing. The LRD process uses pattern matching to link the disparate literatures.

For example, a disease of interest may have hyperinflammation, hypercoagulation and hypoxia as its main characteristics. In that case, the non-disease of interest literature would be searched for records that contain various combinations of hyperinflammation, hypercoagulation and hypoxia. If the purpose of the search is to identify novel treatments for the disease of interest, then substances/behaviors (in the retrieved records) that reduce hyperinflammation, hypercoagulation and hypoxia would be viewed as candidate treatments for the disease of interest. If the purpose of the search is to identify novel CFs for the disease of interest, then substances/behaviors (in the retrieved records) that increase hyperinflammation, hypercoagulation and hypoxia would be viewed as candidate CFs for the disease of interest.

The characteristics mentioned above can be specified at a number of different hierarchical levels of detail. Consider inflammatory bowel disease (IBD), which encompasses chronic inflammatory GI disorders categorized most commonly as Crohn's disease (CD) and ulcerative colitis (UC). IBD is described in more detail in prior studies (2,48). A previous IBD treatment repurposing study by the first author and colleagues mainly used specific biomarkers and their desired directions of value change (e.g., reduce IL-β AND/OR reduce IL-6 AND/OR reduce C reactive protein, etc.) as the pattern to identify records that may contain novel IBD treatments (48).

In a recent IBD-COVID-19 CF commonality study (2), the authors used a much more general biomarker specification

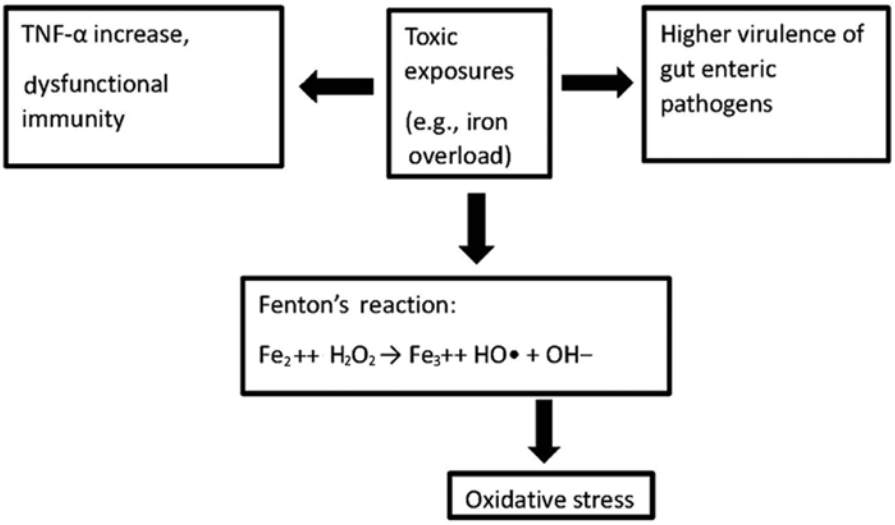

Figure 1. Iron overload alters the immune system by promoting TNF-α secretion (35,36), induces oxidative stress by generating the powerful hydroxyl radical (37), and promotes the replication and virulence of gut pathogen microbiome (38).

as the pattern to identify records that may contain novel COVID-19 CFs not identified previously in the COVID-19 core literature. The encompassing characteristic of the COVID-19 core literature was viewed as immune system dysfunction. This broad characteristic was used as the pattern for searching the non-COVID-19 biomedical literature for records that contained biomarkers and symptoms of immune system dysfunction and associated substances/behaviors. Specifically, the non-COVID-19 immune system dysfunction literature was searched for candidate CFs identified from the dot-product approach (intersection of lists of known toxic stimuli with phrases in the literature of interest) applied to the IBD core literature. If the retrieved records contained biomarkers and symptoms reflective of immune system dysfunction, these candidate CFs became validated CFs for COVID-19. As demonstrated in Appendix S1, the LRD approach used for the present study contains terms both at the specific biomarker level and at the much more encompassing general biomarker level.

Identification of CFs common to GIC and COVID-19. The present study used three separate literatures to identify CFs common to GIC and COVID-19 (see Appendix S1 for the queries used to retrieve these three literatures). First was a mature GIC core literature spanning 1990-early 2021, and it was used to identify CFs that had a direct impact on GIC (i.e., the CF was contained in a GIC core literature record(s). Second was a predominately nascent COVID-19 literature (whose main component was focused strictly on COVID-19 and was primarily ≤9 months old, and whose very minor component included other coronaviruses), and it was used to identify CFs that had a direct impact on COVID-19. Third was a mature literature linked to, but not contained within, the COVID-19 core literature. This linked literature was used to identify CFs that had an indirect impact on COVID-19, and was called the discovery literature. These latter CFs affected the entities that linked this related literature to the COVID-19 core literature. For example, if a key characteristic of the COVID-19 core literature is immune system dysfunction, and immune system dysfunction is a link to this third literature, then a CF to immune system dysfunction identified in the third literature, but not contained in the COVID-19 core literature, has the potential to impact COVID-19 indirectly through the immune system dysfunction link from the non-COVID-19 literature to the COVID-19 literature.

Commonality was determined between i) CFs that impacted GIC directly; and ii) CFs that impacted COVID-19 directly and indirectly using a streamlined dot-product approach to identify the CFs that impacted COVID-19 and GIC directly, and a literature-related discovery approach to identify the CFs that impacted COVID-19 indirectly. Modifiable CFs that contribute to both GIC and COVID-19 were identified.

The COVID-19 core literature was viewed as insufficient for the identification of the COVID-19 CFs due to its nascency and immediacy. The main emphases of the COVID-19 core literature titles are the following: i) Containing the pandemic; ii) identifying the major abnormal biomarker values and symptoms of patients hospitalized with COVID-19; iii) repurposing and testing treatments; iv) developing and testing vaccines; v) assessing the effects of the pandemic on behaviors, medical treatments and procedures; and vi) reviews of treatments, vaccines, restrictions, etc. In brief, the COVID-19 core literature as of early March, 2021, was mainly focused on disease/viral containment rather than prevention.

As of March, 2021, there has been insufficient time to conduct the lengthy laboratory experiments relating CFs to COVID-19 or to conduct the longer-term epidemiological studies required to reveal these associations. Therefore, a more mature intermediate literature that shares commonalities with important aspects of the COVID-19 core literature, and includes the longer-term studies that can demonstrate links of immune system dysfunction consequences to CFs, is required. While the results of the present study demonstrate a substantial number of GIC and COVID-19 direct impact CFs that overlapped, it was considered that far more overlaps between GIC and COVID-19 were possible using the discovery approach. This was the purpose of the third (discovery) literature that was generated.

There were three general themes of articles retrieved from the third (discovery) literature associated with potential CFs for impacting COVID-19 indirectly, although not every third literature article retrieved reflected each theme (some articles reflected only one of the themes; some reflected two, and some reflected all three). The first was increasing vulnerability to infectious disease; the second was exacerbating the seriousness of an existing infectious disease; the third was adversely impacting biomarkers that reflected coagulation, hypoxia, etc., as well as biomarkers that reflected immune system dysfunction. All else being equal, the prioritization of the selection of the potential discovery CFs for inclusion in the present study followed the order above.

There is no guarantee that a CF that produces any one of the three adverse effects listed above, or all three simultaneously, will have the same adverse impact for COVID-19. The reasoning for selection is that if the CF had this adverse effect, or a combination of adverse effects, for another infectious disease, there is greater likelihood that it could have a similar effect on COVID-19, all else being equal. The potential COVID-19 adverse effect(s) need(s) to be demonstrated in an experiment/clinical trial.

Myriad types of commonalities between GIC and COVID-19 beyond CF commonality. In 2014, the first author published a study demonstrating theme commonalities between Parkinson's disease (PD; neurodegenerative) and CD (autoimmune) using phrase matching and bibliographic coupling (shared references) between the two disease literatures (50). Due to the strong emphasis on shared references, the commonality of PD and CD at a more fundamental mechanism level was demonstrated. Combining these two approaches for identifying commonality (CF commonality and bibliographic coupling/phrase matching) could provide deeper understanding at different levels of commonality between GIC and COVID-19.

Data and methods

Dot-product approach. The streamlined method used to identify common CFs that impact GIC and COVID-19 directly (these are CFs that are found in the core literatures for GIC and COVID-19) for the present study is termed a dot-product approach (1,2). Lists of known toxic substances were aggregated from myriad (mainly) government agencies, and combined with lists of CFs identified in our previous disease studies (7,8). This combination produced a final list of >13,000 CFs potentially impacting disease. While this is certainly a large number of potential CFs, it undoubtedly omits additional CFs that a well-resourced study could have identified.

A core literature query was defined for GIC, applied to PubMed, and the resultant retrieval (~275,000 records with abstracts, covering the period between 1990-early 2021) was imported into VantagePoint (VP) text analysis software (www.theVantagePoint.com; V12 Pro/64). This GIC core literature query is shown in Appendix S1. The title and abstract phrases of the retrieved records were parsed in VP, resulting in lists of numerous phrases. The same procedure was followed for the COVID-19 core literature (~88,000 records with abstracts, covering the period between 1990-early 2021); the COVID-19 core literature query is also shown in Appendix S1.

The external list of >13,000 phrases of potential CFs was intersected with the parsed list of abstract phrases in the GIC and COVID-19 core literatures to generate the subset of the 13,000+ phrases relevant to each core literature. There were ~4,400 candidate CFs that impacted GIC directly, and ~2,800 candidate CFs (candidate means they are potential CFs, but need to be validated as actual CFs) that impacted COVID-19 directly. These two intersected lists of direct impact CFs were compared, and the candidate direct impact CFs in common between GIC and COVID-19 were identified. Approximately 2,250 candidate direct impact CFs in common were identified, albeit some being variants of the same concept. However, this is a very conservative estimate of candidate direct impact CFs in common, for the reasons shown in Appendix S2.

LRD approach. The dot-product approach described above produced CFs that impacted GIC and COVID-19 directly (using articles contained in the core literatures only). However, as the numbers above indicate, there were ~2,150 CFs that impacted GIC directly, but did not impact COVID-19 directly. The myriad reasons for CF underestimation summarized in Appendix S2 could explain this observation, particularly given the nascency of the majority of the COVID-19 core literature relative to the time required to demonstrate CF-disease linkages in laboratory experiments. This led to the decision to include an approach for identifying CFs that impacted COVID-19 indirectly.

One method for identifying indirect impacts of CFs on a given disease is with use of the discovery component of LRDI. This has been used successfully to generate CF discovery in chronic kidney disease (CKD) (8) and Alzheimer's disease (AD) (7). It has also been used to generate treatment discovery (treatment repurposing) for CKD (8) and AD (7), as well as for IBD (34). A variant of this discovery approach was developed for the present study.

In previous studies, patterns of biomarkers, symptoms, etc., in a disease core literature that were associated with that disease were extracted and applied to the larger non-disease literature to identify substances and behaviors that produced these patterns (7,8) (as described in the Introduction). Following the analyses of the retrievals, a number of these substances and behaviors were classified as potential CFs to the disease of interest, and needed to be validated through experiments and/or epidemiological studies. There were no constraints placed on the substances and behaviors.

The present study aimed to select, from the ~2,150 substances and behaviors, CFs impacting GIC directly and not impacting COVID-19 directly. The study also aimed to ascertain whether evidence existed in the non-COVID-19 literature to validate that at least some of the substances selected could be viewed as candidate CFs for indirect impact of COVID-19 (CF discovery, or CF repurposing, analogous to treatment repurposing). The present study used a modified version of recent discovery queries previously demonstrated (49) that required retrievals to contain the CF under consideration (this modified version of the discovery query is shown in Appendix S1). For purposes of completeness, this approach was eventually applied to all the CFs selected for display purposes, and the results are presented in Table II.

Selection of candidate common CFs for validation. The phrases in common between GIC and COVID-19 should be

Table II. Common contributing factors to GIC and COVID-19.

Contributing factor (from dot-product)	Cat.	Impact on COV	(Refs.) GIC	COV	Disc
Advanced glycation end products	1	D	(53)	(74)	(75)
Alcohol consumption	1	D	(76)	(77)	(78)
Circadian disruption/poor sleep	1	D	(79)	(80)	(81)
High temperature cooking	1	I	(82)		(83)
High-fat diet	1	D	(84)	(85)	(86)
Malnutrition	1	D	(87)	(88)	(89)
Nitrosamines	1	I	(90)		(91)
Red meat	1	D	(92)	(93)	(94)
Sedentary/physical inactivity	1	D	(95)	(96)	(97)
Smoking	1	D	(98)	(99)	(100)
Sodium intake	1	D	(101)	(102)	(103)
Substance abuse/morphine/cocaine/opioids/ heroin/methamphetamine	1	D	(104)	(105)	(106)
Vitamin D deficiency	1	D	(107)	(108)	(109)
Western diet	1	D	(110)	(111)	(112)
Bone marrow transplantation	2	D	(113)	(114)	(115)
Liver transplantation	2	D	(116)	(117)	(118)
Omeprazole/proton pump inhibitors	2	D	(119)	(120)	(121)
Ovariectomy	2	D	(122)	(123)	(124)
Radiotherapy	2	D	(125)	(126)	(127)
Renal transplantation	2	D	(128)	(129)	(130)
Cytomegalovirus	3	D	(131)	(132)	(133)
Herpes simplex virus	3	D	(134)	(135)	(136)
Mycotoxins	3	D	(137)	(138)	(139)
Aluminum	4	I	(140)		(141)
Arsenic/As	4	D	(142)	(143)	(144)
Asbestos	4	I	(145)		(146)
Benzene	4	D	(147)	(148)	(149)
Benzidine	4	D	(150)	(151)	(152)
Bisphenol A	4	D	(153)	(154)	(155)
Cadmium/Cd	4	D	(156)	(157)	(158)
Carbon dioxide/CO_2/CO(2)	4	I	(159)		(160)
Carbon tetrachloride	4	I	(161)		(162)
Chlordane	4	I	(163)		(164)
Chlorinated drinking water	4	D	(165)	(166)	(167)
Chloroform	4	I	(168)		(169)
Chlorpyrifos	4	I	(170)		(171)
Chromium/Cr	4	D	(172)	(157)	(173)
Crude oil	4	I	(174)		(175)
Di(2-ethylhexyl) phthalate	4	I	(176)		(177)
Heterocyclic amine	4	I	(178)		(179)
Ionizing radiation	4	D	(180)	(29)	(181)
Mercury/Hg	4	D	(182)	(157)	(183)
Microplastics	4	I	(184)		(185)
Nanoparticles	4	D	(186)	(187)	(188)
Nickel	4	I	(189)		(190)
Nitrate	4	D	(191)	(192)	(193)
Nitrite	4	D	(194)	(192)	(195)
Nitrogen dioxide/NO_2/NO(2)	4	D	(196)	(197)	(198)
Organochlorines	4	I	(199)		(200)
Organophosphates	4	D	(201)	(202)	(203)

Table II. Continued.

Contributing factor (from dot-product)	Cat.	Impact on COV	(Refs.) GIC	COV	Disc
Ozone	4	I	(196)		(204)
Pb	4	D	(205)	(32)	(206)
Perfluorooctanoic acid	4	I	(207)		(208)
PM(10)/PM10	4	D	(209)	(210)	(211)
PM(2.5)/PM2.5	4	D	(196)	(212)	(213)
Polychlorinated biphenyls/PCBs	4	I	(199)		(214)
Polycyclic aromatic hydrocarbons	4	D	(215)	(216)	(217)
Silica	4	D	(218)	(219)	(220)
Talc	4	I	(221)		(222)
TCDD (2,3,7,8-tetrachlorodibenzodioxin)	4	D	(223)	(166)	(224)
Trichloroethylene	4	I	(225)		(226)
Chronic stress	5	D	(227)	(228)	(229)
Restraint stress	5	I	(230)		(231)

GIC, gastrointestinal cancer; Cat., category; COV, coronavirus 2019 (COVID-19); D, direct impact; Disc, discovery; I, indirect impact.

viewed as candidate CFs, which must be validated as actual CFs by detailed analysis. There was also the question of how many validated CFs are required to support the hypothesis of common causation between the two diseases. There are two main criteria to be considered in making the selection. The first criterion is the numbers of CFs in common. The second criterion is the importance of the CFs in contributing to the disease.

In the case that the system operation is determined mainly by a few significant factors, as in a number of large and complex systems, then a handful of such significant factors is all that would be required to support the hypothesis. If no such significant factors stand out, then further CFs would be required to support the hypothesis of common cause.

For GIC and COVID-19, there were significant factors that stood out, and these were the foundation of the validation selection process. A balance/trade-off between the two major selection criteria resulted in the selection of 63 common phrases between GIC and COVID-19 to be validated as CFs. These 63 phrases included those deemed most significant and spanning the five-category taxonomy we have developed for classifying modifiable CFs to disease: Lifestyle, iatrogenic, biotoxins, occupational/environmental, psychosocial/socioeconomic (7). Genetics was not included, since the CFs in the current definition were viewed as modifiable, indicating that they were relatively controllable.

Given the shortcomings of the COVID-19 core literature from the perspective of insufficient causation studies (as described above), the present study also included CFs that impacted COVID-19 indirectly. This would also demonstrate the novel CF discovery technique developed for the present study. In total 21 of the 63 candidate CFs were selected as indirect impact CFs and validated as proof of concept. A schematic diagram of the study protocol and approach used is presented in Fig. 2.

Results

The 63 GIC direct impact CFs in common with the COVID-19 direct and indirect impact CFs selected for validation are presented in Table II. The detailed record excerpts demonstrating the links between the CFs and disease are presented in Appendix S3.

Table II contains six columns. The first (leftmost) column (CF) is the CF that was validated. The second column contains the category to which the CF is assigned (1, lifestyle; 2, iatrogenic; 3, biotoxin; 4, occupational/environmental; and 5, psychosocial/socioeconomic). The third column signifies whether the impact of the CF on COVID-19 was direct or indirect. The fourth, fifth and sixth columns contain the references that link each CF to the biomarkers, and are presented in the order of GIC literature, COVID-19 literature and discovery literature. If a CF listed in the first column has no reference listed in the fifth column, then it was not a COVID-19 direct impact CF, and the reference in the sixth column reflects a validated discovery (the listed CF impacts COVID-19 indirectly). If a CF listed in the first column has a reference in the fifth column, then it was a COVID-19 direct impact CF, and the reference in the sixth column reflects a confirmed discovery [it was a validated discovery prior to 2020, and became a confirmed discovery in 2021 when proof of direct linkage became available in a record(s)].

Discussion

The results of the present study conclusively demonstrate the wide range of CFs in common between GIC and COVID-19. The next section addresses some of the numerous mechanisms considered responsible for these links, followed by a section that demonstrates how these common CF results provide the basis for a unified theory of infectious and chronic disease.

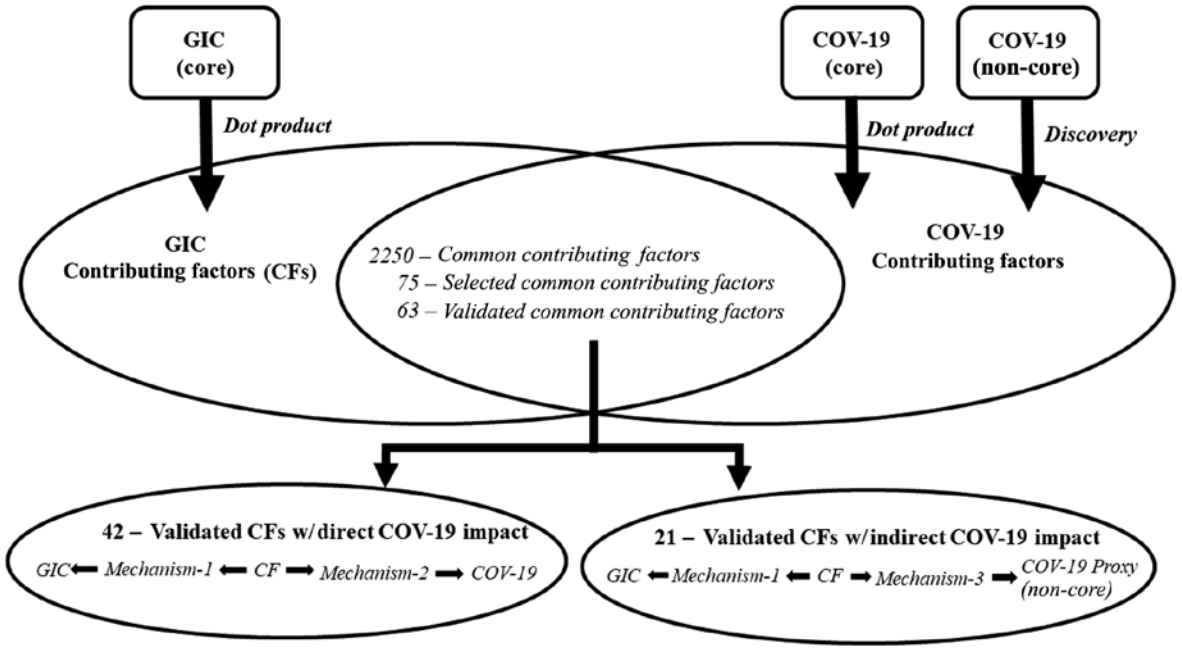

Figure 2. Schematic diagram of the study protocol and approach used to identify the contributing factors common to gastrointestinal cancer (GIC) and COVID-19 (COV-19).

The operational implication of the results is that strengthening the immune system against both infectious and autoimmune diseases requires the discipline to i) remove exposure to a broad range of toxic substances; and ii) eliminate toxic behaviors.

Mechanisms that link CFs with GIC and COVID-19. It would be of interest to determine some of the mechanisms that link CFs identified in the present study with GIC and COVID-19. The following brief analysis examines the role of advanced glycation end products (AGEs), high-fat diets (HFDs), cooked red meat, excessive alcohol consumption and a sedentary lifestyle in contributing to, and/or exacerbating, GIC.

A dietary context appears to contribute to and sustain the global burden of GICs (51). Among the CFs, a main role is played by AGEs that can activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome (52). This not only determines the colonic inflammation environment for carcinogenesis (53), but also impairs innate immune response in macrophages (35), thereby contributing to the tumor escape from innate immunosurveillance (54,55).

A potent carcinogenic stimulus is also provided by HFDs (55,56). Mechanistically, HFDs predispose an inflammatory scenario by inducing a systemic chronic low-grade inflammation (57) characterized by the elevated production of the pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α (58), in the gut. Again, the inflammatory trigger is represented by the activation of the NLRP3 inflammasome (59), with saturated fatty acids favoring NLRP3 inflammasome activation (60) and unsaturated fatty acids impeding NLRP3 activity (61,62).

Another crucial dietary CF in GI carcinogenesis is represented by the consumption of high amounts of cooked red meat. Indeed, consuming red meat equates to introducing hemoglobin and its degradation products, heme and iron, in non-hematopoietic tissues (63). Iron can generate severe oxidative stress via the Fenton reaction, thus causing severe inflammatory pathologies and eventually leading to cancer (63-65). Moreover, the iron load is a crucial factor in colorectal carcinogenesis as it can trigger the macrophage expression of TNF-α-converting enzyme (TACE; also known as ADAM17) (66,67). The tolerable iron upper intake level (UL) for adults is 45 mg/day of iron, a level based on gastrointestinal distress as an adverse effect. The median dietary intake of iron is ~16-18 mg/day for males and 12 mg/day for females (https://www.ncbi.nlm.nih.gov/books/NBK222309/).

TACE is a sheddase (membrane-bound enzyme) that cuts and sheds the membrane-bound precursor of TNF-α to its mature soluble form (68). In other words, a cytokine storm is unleashed, given that TNF-α is the master regulator of inflammatory cytokine production (69).

Such a sequence of potent inflammatory events can be further enhanced by alcohol consumption. In fact, the iron-induced oxidative stress and inflammation are potentiated by excessive alcohol abuse that results in further dysregulated iron homeostasis at the hepatic level and heightened TACE induction and activity (66).

In this pathological scenario dominated by inflammation and oxidative stress, a sedentary lifestyle also plays a role. Indeed, sedentary behavior relates to chronic inflammation and colorectal cancer development, while physical activity plays a protective role (70,71). The molecular basis of the protection exerted by physical activity appears to reside in a transcriptional factor, the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α), the level of which is enhanced by physical activity (72). In fact, PGC-1α regulates proteins involved in the antioxidant defense and lowers the expression of inflammatory markers (73).

On the whole, these five CFs, namely AGEs, HFDs, red meat, alcohol consumption and sedentary behavior, suffice to

explain much of the 2018 epidemiological data reporting an estimated 4.8 million new cases of GICs and 3.4 million related deaths worldwide, with GI cancers accounting for 26% of the global cancer incidence and 35% of all cancer-related deaths (51).

Unified theory of infectious and chronic diseases. The present study is the third one by the first author and colleagues examining the CFs common to COVID-19 and a chronic disease (1,2). As time has proceeded, and the COVID-19 core literature has increased in size, other CFs linked to COVID-19 have emerged and commonality of CFs to chronic disease has increased. This trend is expected to continue.

All three studies have demonstrated the existence of numerous potential CFs common to the two types of disease, and at least 50 common CFs have been validated in each study. Many of the common infectious disease-chronic disease CFs are also common among the three studies. For the CFs that have been validated, myriad common factors include lifestyle (e.g., dietary content, vitamin and mineral deficiencies, food processing and preparation, exercise, sleep, substance abuse, etc.), occupational/environmental (air pollution, water pollution, heavy metals, agrochemicals, occupational chemicals, ionizing and non-ionizing radiations, etc.), and psychosocial/socioeconomic (myriad forms of stress, adverse childhood experiences, isolation, low income, etc.) factors. Iatrogenic factors are mixed; substances/radiations that are beneficial for treating one disease may exacerbate other diseases. Biotoxins are mixed as well, particularly since some viruses associated with disease enhancement are also used as vectors for drug/treatment delivery.

In the case that the majority of the important CFs to COVID-19 are important CFs to the associated chronic diseases examined, as increasingly appears to be the case with the growth of the COVID-19 literature, the question remains of what could be concluded about the similarity of these infectious and chronic diseases.

One important conclusion is that for the prevention of either type of disease, the CFs identified and validated must be eliminated/reduced as broadly, deeply, and rapidly as possible.

A second important conclusion is that, if it is assumed that the symptoms characteristic of either disease represent the host's response to the CFs, the same fundamental disease can have myriad manifestations exhibited through the symptoms. Thus, treating the host's manifestation of the disease (symptoms) is different from treating the disease. The manifestations can be suppressed, but the disease perseveres. Only elimination of the CFs, as outlined in the previous paragraph, has the potential to eliminate the disease (and its associated damages) at its core (assuming that the damages resulting from the disease are not irreversible and the host does not have a strong genetic predisposition to the disease).

There may be treatments for COVID-19 and GIC that overlap; however, there may also be treatments that are antagonistic. As demonstrated in prior sections and the biomedical literature (39-45), inflammatory and coagulation factors exhibit clinical manifestations in both COVID-19 and GIC. Treatments that reduce inflammation and coagulation should be beneficial to both diseases, and could possibly overlap. Conversely, immunosuppressants (used in myriad cancer treatments) tend to increase vulnerability to infectious diseases. In general, if the removal of a potential cause is defined as one type of treatment, then one potential class of overlapping treatments will be the removal of the CFs in common between GIC and COVID-19.

The third conclusion relates to the different external manifestations of disease, even though the CFs have a strong commonality. In the case of the existence of a high commonality between the CFs to GIC and COVID-19, the question would arise as to why one group of individuals manifests COVID-19 symptoms and another group manifests GIC symptoms (although in actuality the vast majority of individuals experiencing the most severe forms of COVID-19 are those with multiple chronic disease comorbidities, exhibiting symptoms of both types of diseases).

There are at least two explanations for this. Individuals have different genetic structures and different predispositions (particularly as regards responses to CFs), and their external manifestations would be expected to differ. Second, CFs have temporal and dosage components (among others), so the CF 'signature' of each individual differs, even following exposure to the same type of CF. As a simple example, one individual who smokes may develop lung cancer, another may develop CD, another may develop myocardial infarction, another may develop COVID-19 and another may remain healthy. In real-life, individuals are exposed to myriad combinations of CFs. Depending on the complex structure of temporal and dosage components of each CF and the nature of interactions among CFs, different external manifestations of the exposure combinations would be expected.

It may be possible that the analysis and treatment of these infectious and chronic diseases have been performed using the wrong 'coordinate system'. These diseases have been viewed from the perspective of their external manifestations (symptoms) rather than the perspective of their CFs. When 'coordinates' are switched from symptoms to CFs, and focus is placed on treatments and preventative measures to alter the CFs rather than the symptoms, a unified approach for resolving the dichotomy between these two types of diseases and, most importantly, eliminating their prevalence, may be presented. Obviously, in the case that symptoms become life-threatening or may result in permanent damage, short-term tactical treatments are required; however, for the intermediate or long-term, preventive measures are necessary.

New paradigm required for preventing and treating infectious and chronic diseases. The findings of the present study suggest a need for a paradigmatic shift in medical approaches to disease. The current approach to both infectious and chronic disease in Western medicine is often external-treatment-based (i.e., providing a drug, vaccine, radiation, surgery, etc.) to reduce symptoms without sufficiently addressing the underlying modifiable factors that enabled the disease to emerge. The present study highlights modifiable factors (toxic exposures and behaviors) that contribute to disease pathogenesis via various mechanisms of immune dysfunction, and demonstrates CF commonality between GIC and COVID-19. Eliminating these factors as comprehensively and rapidly as possible is prudent, and perhaps should be pursued in parallel with treatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and in the supplementary material.

Authors' contributions

RNK contributed to the conception of the study, as well as in data analysis and in the writing of the manuscript. MBB participated in data analysis, validation of the results, and in the preparation of the tables. DK participated in data analysis and in the writing of the manuscript. DRS contributed to query development, background development, and in the writing and editing of the manuscript. LK contributed to data analysis, as well as in the study design, and in the writing, and editing of the manuscript. ALP contributed to the conception and design of the study, as well as in the writing and editing of the manuscript. ND contributed to the design of the study, as well as in the drafting, writing and editing of the manuscript. AT contributed to the critical revision of the study, as well as in the design, drafting writing, and editing of the manuscript. DAS contributed to the design of the study, as well as in the revision, writing and editing of the manuscript. RNK and MBB confirm the authenticity of all the raw data. All the authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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