UNDERSTANDING THE THYMUS WITH APPLICATIONS TO COVID-19 PATHOPHYSIOLOGY AND SUSCEPTIBILITY WITH POTENTIAL THERAPEUTICS

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus continues to severely impact health and economies around the world. However, the underlying mechanisms behind the disease are still under investigation. Of particular interest to the scientific community is the reason why children typically experience much less severe symptoms when infected by COVID-19. The mild clinical course in the pediatric population suggests that age-related factors affecting host susceptibility may hold the key to better understanding the disease. Based on our extensive review of the literature on SARS-CoV-2, as well as on the diversity of the immune system as a function of age, we hypothesize that the thymus may play a significant role in explaining the above phenomenon. Namely, we propose a hypothesis that thymic output and therefore a lack of diversity of T-cell receptor (TCR) affinity is causally linked to SARS-CoV-2 susceptibility. Statistical analysis of epidemiological data from Canadian COVID-19 infections is provided in support of this theory. Furthermore, the lymphopenia (an abnormally low level of lymphocytes in the blood) observed in severe clinical cases of SARS-COV-2 can be explained by a delay in activation of the adaptive immune system, due in part to the rarity of SARS-CoV-2 specific clonotypes being maintained in the lymph nodes and blood. Non-specific (with respect to TCR) chemokine signaling in the absence of clonal expansion of T-cells would present as lymphopenia in a respiratory infection. We also note that there are existing agents, such as thymosin-α-1-Fc (TA-1) that have been shown to augment the bioavailability of naive CD8+ and CD4+ cells that have undergone V-D-J-recombination. We therefore suggest that TA-1 can have a therapeutic effect in COVID-19 patients by stimulating the production of additional diversity of T-cell receptor affinity and facilitating the production of T-cell clonotypes specific to SARS-CoV-2 epitopes, as well as priming dendritic cells by increasing the expression of co-stimulatory molecules. Furthermore, the lack of type 1 interferon response suggests that a combination of TA-1 and $\alpha\beta$-interferon may provide the synergistic effects necessary to effectively engage the adaptive immune system in a timely manner, where deemed appropriate by the treating physician.

1 Introduction

The adaptive immune system has evolved over the course of millions of years to manage infections by a wide range of microorganisms, including the most current and imminent threat posed by SARS-CoV-2 virus. SARS-CoV-2 is thought to have originated from a zoonotic transmission [5] and previous research had identified a SARS-like virus as a potential threat in a Chinese bat population in 2015 [38]. A notable clinical manifestation of a severe case of COVID-19 is lymphopenia, associated with poor outcomes [62]. Understanding the cause of lymphopenia (a low

abundance of lymphocytes in the blood) is crucial to understanding SARS-CoV-2 pathogenesis and to developing a successful treatment.

A key element of mounting an effective adaptive response involves maintaining an adequately diverse and numerous pool of T-cells capable of responding to novel antigens [44]. The generation and selection of naive T-cells is an extremely efficient system that has evolved to provide a balanced reaction which minimizes harm to the host [47]. The diversity of the clonotypes with respect to TCR composition being maintained is an important measure of the host's ability to respond to antigenic challenges [44]. The number of bio-available cells capable of responding to a specific antigenic challenge influences the magnitude of the immune response. This crucial element of the host response to viral infections involves the creation of a pool of memory T-cells, capable of quickly responding in large numbers with repeat exposures. We propose that a plausible explanation for the age-specific susceptibility to novel antigenic fitness challenges is a decrease in diversity of receptor affinity, maintained in part by the thymus, which decreases exponentially with age in terms of both size and output [49]. More specifically, it is the number of available T-cells and their diversity which together help ensure a successful host defense. The fact that children appear to have a milder clinical course of COVID-19 [24] suggests that the problem is not the virus but rather one of the aging host. This is supported by the low type 1 interferon response measured in SARS-CoV-2 infected cells [68] which should be interpreted as a lack of early deleterious effects.

In addition to age-related involution and the associated decreased function of the thymus, the hormones which regulate mammalian thymic output become imbalanced in certain pathological conditions such as metabolic syndrome or obesity [73, 51]. This hormonal imbalance affects the thymic output and results in a less diverse bioavailable T-cell repertoire. This makes an individual more susceptible to novel antigenic challenges like certain cancers [15] and perhaps SARS-CoV-2. In fact, both obesity and metabolic syndrome have been shown to be associated with poor outcomes in COVID-19 disease [29, 75]. In a very novel viral infection where the virus-specific clonotypes have not been maintained in large quantities, a lack of diversity would delay the presentation of peptides by dendritic cells (DCs) to a sufficient number of virus-specific T-cells. Cellular immunity has been shown to be efficient in SARS-CoV-2 infection as a result of the lack of seroconversion in certain familial COVID-19 cases [19].

In this paper we review the potential role of the thymus as a causal factor in inducing susceptibility to COVID-19. A plausible explanation for the lymphopenia observed in severe clinical cases of SARS-CoV-2 is provided and furthermore, we suggest that Thymosin-α-1-Fc, with the possible addition of type I Interferon, be considered to help initiate the adaptive response by increasing the number of T-cells with naive diversity made available in the blood through thymic output. Recent clinical data, made available subsequent to the development of this hypothesis, showed that TA-1 had been efficient at reducing mortality [31]. We suggest that this outcome may be the result of a more efficient initial engagement of virus-specific clonotypes by involving the highly efficient innate arm of the immune system evolved to respond to viral challenges in a balanced way.

2 Review

2.1 Thymus and T-cell generation

The thymus is a key component of the immune system, specifically in terms of the development of cellular immunity [41]. The thymus is primarily responsible for producing naive T-cells with a diverse range of functions and TCR compositions [65]. This stream of constant diversity of naive T-cells is important in responding to molecular patterns that the immune system has never encountered before as these cells would not have undergone clonal expansion in the absence of activation. A feature of this adapted cellular defence mechanism is the creation of an abundance of memory T-cells in response to a successful adaptive response to a viral antigenic challenge. These memory cells are capable of quickly responding to recurrent antigenic challenges of a similar nature in terms of the molecular patterns of the proteins to be identified. The diversity in the naive T-cell population is generated through V-D-J and V-J recombination in the thymus which allows thymocytes to generate T-cell receptor (TCR) diversity through alternative splicing [21, 10]. The thymus is the organ within which diversity can be safely developed without risking an auto-immune reaction, since the thymocytes expressing TCRs that bind to tissue-specific antigens are removed [25].

This diversity of affinity is achieved by a tightly regulated selection process in the thymus, facilitated in part by the binding of T-cell receptors to major histocompatibility complex (MHC) sites and Autoimmune Regulator (AIRE) genes which make available tissue-specific self-antigens to developing thymocytes [6]. T-Cells that recognize certain host-specific tissues are, for the most part, removed [69]. Most thymic naive T-cells have undergone V-D-J recombination [67] which generates a *random* distribution of TCRs not yet subject to selection/deletion due to competition within the lymph nodes. There is a qualitative difference in the patterns maintained in the lymph nodes and the ones generated by this process. The Recombination activating gene (RAG) is necessary for this recombination, and its deficiency leads to immune disorders as the development of functional T and B cells is not possible [16]. The involution of the thymus,

associated with a reduced output of naive T-cells [69], has been suggested to be a result of a hormonal mechanism regulated in part by the production of hormones such as progesterone (PG) [66], growth hormone (GH), ghrelin (GR) [63], and possibly estrogen [35].

The reduction in thymic output is progressive throughout life but exponential in nature, accelerating after 60 years of age in men and again after 80 years of age in both men and women [42]. The effect of this sharp decrease in thymic output on T-cell receptor diversity in the peripheral T-cell pool is an ongoing subject of investigation [7]. A key step in assessing thymic contribution to the available T-cell pool is differentiating naive T-cells produced in the thymus from those resulting from peripheral naive T-cell replication. Recent thymic emigrants (RTEs) can be distinguished from naive T-cells produced via extra-thymic cell division by the presence of T-cell Receptor excision circles (TRECs) [2]. TRECs are formed in the DNA of thymocytes [59] during V-D-J recombination in the thymus [2]. Naive T-cells produced in the periphery as a result of cell division do not undergo V-D-J recombination and therefore do not possess TRECs. The difference in diversity from these two sources of naive T-cells may influence the susceptibility to certain diseases, which include SARS-CoV-2 as well as certain cancers, as their age-stratified prevalence seems to follow an exponential trend very similar to that seen in the involution of thymic output [49]. RTEs were once thought not to be important after adolescence as a result of extra-thymic maintenance of the naive T-cell pool [7]. However, studies have shown that RTEs continue to contribute to the diversity of the peripheral T-cell repertoire throughout the course of life in terms of receptor distribution and function [25, 65]. Furthermore, sophisticated methods have recently been developed to distinguish the TRECs produced in the thymus from peripherally maintained ones. These methods have confirmed a reduction in thymic production with age, more prominent in men than women for most decades [42]. There has been limited appreciation of the role of age-associated thymic involution with respect to clinical pathophysiology in the past, but more recent work is beginning to suggest a greater clinical impact [49, 36, 73].

2.1.1 T-cell maturation

The maturation of T-cells occurs in lymph nodes through a selection mechanism which favours frequently activated clonotypes as a result of cell division following activation and a competition for limited survival signals from molecules like IL-7, IL-15 [30, 32] and interactions with peripheral MHC sites [8]. The combination of thymic output, lymph node maintenance, there exists balance of diversity and specificity. In aging lymph nodes, not only is there an oligoclonal population of T-cells in terms of TCR diversity but these cells have matured into specific subtypes, optimized for frequent antigenic challenges [27]. There is a trade-off between diversity and specificity in the immune system. This trade-off favours diversity in the young when the immune system must be able to respond to a variety of challenges, and specificity in the aging population when the immune system becomes senescent and highly specialized.

2.1.2 Maintenance of diversity

After reaching adulthood, the thymus is not thought to contribute T-cells to the lymph node population [17]. However, according to some mathematical models, the daily thymic output of a healthy adult is $10^7 - 10^8$ T cells per day and is roughly equal to the number of β-clonotypes in the lymph nodes [50] estimated at approximately 10^8. Our immune system has evolved under selection pressure, and therefore, one would expect an optimal balance near sexual maturity. This balance is seemingly tested by zoonotic viruses which often pose a risk to people whose immune systems have no training or those whose immune systems are senescent.

2.2 Viral Response

The innate system is the first responder in the early detection of a pathogen and is a crucial player in host response. The initial detection of pathogen-associated molecular patterns (PAMPs) through pattern-recognition receptors (PRRs) on dendritic cells initiates various signalling pathways [43]. Following detection of pathogens, PRRs mediate several immune responses including the release of pro-inflammatory cytokines and various anti-microbial responses [4]. Notably, the type I and type III interferon (IFN) response is central to the host defense in a viral infection [40]. SARS-COV-2 is known to elicit a very low type I IFN response and as such does not immediately engage the host defense [1]. These cytokines aid in the antiviral response by helping to inhibit viral replication [9]. IFN-γ has been found to inhibit viral activity as well as aid T helper cells [58]. Dendritic cells take up and process antigenic peptides to present epitopes on their cell surface [11]. The adaptive immune response consists of antigen specific T and B cells. Dendritic cells present viral peptide epitopes to T cells either through MHC class I for CD8+ cytotoxic T cells or MHC class II for CD4+ T-helper cells [61]. Following costimulatory signals, activated T cells hone back to the site of infection using a trail of chemokines secreted by resident macrophages. Naive CD4+ T cells differentiate into various subset effector cells following priming and cytokine stimulation [61]. Activated CD4+ T cells can mediate improved immune response by interacting with CD8+ T cells and B cells [61]. Notably, TH1 cells play a pertinent role

in an antiviral response, releasing pro-inflammatory cytokines such as IFN-γ and upregulating markers associated with granzymes leading to cell-induced apoptosis [53].

A delicate balance of T-cells is required to mount an effective and balanced immune response including cytoxic CD8+ T-cells and CD4+ helper T-cells. They are critical to mediate viral clearance through apoptosis utilizing Fas and Fas Ligand, TRAIL (TNF-related apoptosis-inducing ligand), and pro-inflammatory cytokines [55]. Following infection, CD4+ and CD8+ memory T cells may be established as well B cells that produce antibodies after interaction with helper T cells. The memory cells and antibodies protect against a secondary infections [55].

2.3 SARS-CoV-2

The SARS-CoV-2 virus, having originated from an animal reservoir, would have undergone many years of selection pressure, rendering the virus less damaging to the host reservoir. Low levels of type I interferon suggest that the virus is not triggering cellular signalling to alert the the body's immune system to a viral threat [64]. However, when the virus encounters an immune system in which it has not evolved, the initiation of immune recognition pathways and subsequent inflammation produce pathogenic dynamics and the manifestation of disease. These zoonotic transmissions often lead to disease in both the young and the elderly as the young lack any memory immunity and the elderly have a senescent immune system.

2.3.1 Lymphopenia in severe COVID-19

Lymphopenia is perhaps the most important and information-carrying manifestation of severe COVID-19 [62]. It suggests that there may be a movement of T-cells from the blood to the lung parenchyma that is greater than the compensation provided by a clonal expansion of T-cells in the lymph node. The insufficiency of clonal expansion may be a result of a delay in presentation of viral epitopes by dendritic cells (DCs) to virus-specific clonotypes, resulting in an increase in the amount of virus escaping initial containment. This leads to more tissue damage, which increases the non-specific recruitment of existing lymphocytes. In this situation, the hyperinflammatory state may be a result of the lack of activation rather than the overactivation of the immune response response but also the result of a lack of sufficient initial response leading to widespread damage which in turn activates the antigen-nonspecific innate immune response that leads to further tissue damage in a forward feedback loop. It is perhaps an odd fact that it is well accepted that this disease is a result of hyperinflammation in the presence of lymphopenia. One would think that the lymphopenia suggests that the inflammatory response is inadequate for the specific affect.

3 Thymic modulation as a therapeutic target

Recent studies have shown that the thymus is a potent target for therapeutic action against a wide range of diseases including certain cancers [14]. This is unsurprising as the thymus can be thought of as the source of immune diversity in the body but, due to the diversity of function in T-cells [48], it can be seen as a means of not only detecting abnormal molecules, but also of preserving homeostasis by generating molecules with similar affinities to ones that have not survived the competition mechanism in the lymph nodes.

3.1 Pregnancy, COVID-19 and the thymus

If thymic output is important in terms of COVID-19 susceptibility, then one would expect the outcome in pregnancy to be worse as the thymus involutes during mammalian pregnancy [54]. It is thought that regulatory T-cells play a protective and immunosuppressive role to allow for fetal development [77] so that the fetus is not rejected [13]. Progesterone is thought to reduce thymic output and to modulate the immune system, which may explain why women do not seem to suffer from the lack of thymic output [28]. One particular study on the outcomes of COVID-19 infections contracted during pregnancy showed an abrupt increase in severity following parturition [12]. The authors of that study attributed this observation to an increase in blood volume, however, the immediacy of the worsening symptoms may be a result of the withdrawal of progesterone secreting cells. The levels of progesterone are known to drop dramatically immediately after pregnancy [26] and as a result, the immunoprotection from progesterone is reduced. Notably, an ongoing clinical trial is investigating this:NCT04365127.

The extent of the reduction of thymic output during pregnancy is still unclear, and the immunoprotective role of progesterone may play a role in suppressing exaggerated innate immune responses. Furthermore, on average, pregnant women are younger and are followed quite closely, and therefore have a higher quality of medical care. The age of the pregnant woman and the immunosuppressive role of progesterone suggest that the impact on the thymus cannot be easily measured with respect to COVID-19 susceptibility and severity as a result of these additional factors.

3.2 Difference in COVID-19 susceptibility between men and women

It is well documented that thymic involution is more prominent in men than in women [23], and this is consistent with the data showing that men have a more severe clinical course of severe COVID-19 than women. A statistical hypothesis test was carried out on the data in Table 5, which involved a 2-sample test for equality of proportions without continuity correction, yielding a p-value of $p < 2.2 \times 10^{-16}$. This result is strong evidence that men are more susceptible to dying when hospitalized than women are, but only weakly supports the hypothesis that thymic output has a causal effect on disease susceptibility, as no measurements of thymic output were taken on this sample. The association in terms of the difference between men and women and the age susceptibility seem to follow the same exponential trend which is seen in thymic involution [49].

3.3 Genetic Analysis of T-cells

A recent study analyzed the differences between exposed and unexposed blood donors in terms of their reactivity to SARS-CoV-2 antigens. It showed a lack of affinity to the spike protein in most of the unexposed donors [22]. The analysis showed that over 50% had some form of reaction to the spike protein in terms of the CD4 cells. This still leaves the possibility that a fair amount of people have no cross-reactivity whatsoever. Furthermore, the key to a successful antiviral defense involves the recruitment of cytotoxic CD8 cells which can recognize proteins being manufactured and degraded and then shown on Major Histocompatibility (MHC) type I sites. The small sample study showed very little cross-reactivity, which can explain how the cell might escape detection in many cases.

Furthermore, if cross-reactivity were the driving factor in host susceptibility, one would not expect to see such a clear exponential distribution favoring the young as seen in Figure 3. In other words, if SARS-CoV-2 were a test of specificity and previous exposure, which was the object of the study in question, one would see a clear advantage for people in their most healthy, reproductive years. This does not seem to be the case for SARS-COV-2; therefore, this cross-reactivity is not thought to be the main causal factor in providing protection against COVID-19 for hospitalized patients.

3.4 TA-1

Thymosin-α-1 has been discovered in the 1970's [20] and is known to empirically increase the amount of TREC-containing T-cells in the blood, subsequent to COVID-19 exposure [31]. This bioavailable population of thymus-derived naive T-cells has a greater diversity of TCRs than the lymph nodes, as a consequence of the generation process and the fact that TCR generation is thought to only happen in the thymus. This provides a broader coverage of potential antigens and greater functional capacity. We suggest that the synergistic effect of $\alpha\beta$ interferon and TA-1 is a mechanistically plausible treatment for COVID-19 when the treatment objective is to activate the adaptive cytotoxic response in a balanced manner.

Genetic studies have pointed to a low affinity of CD8 cells to the spike protein, but small sample sizes limit the possible inference [22]. The goal of this treatment is to ensure that there is a balance between the destruction by the cytotoxic lymphocytes and the immunosuppression that is eventually engaged to prevent excessive harm to the host.

Furthermore, TA-1 has shown some efficacy in the treatment of sepsis [72], where a similar relationship between low lymphocyte count and mortality has been observed [56]. The full mechanism remains unclear; however, TA-1 has been shown to upregulate co-stimulatory molecules CD40 and CD80 and increase the expression of Toll-like Receptors [52]. In severe COVID-19 patients, Tim-3 and PD-1 markers have been observed on T-cells, which is suggestive of ineffective viral containment and cell-line exhaustion [76]. A recent review article presented the results of a genetic analysis of broncheoalveolar lavage fluid (BALF) [39] from patients with different outcomes with respect to SARS-CoV-2 infection survival. Specifically, a higher proportion of CD8+ T-cells with tissue resident signature in the BALF of patients was associated with a mild course of the disease [39]. The suggestion was that a higher proportion of infiltrating mononuclear phagocytes was associated with hyperinflammatory states and higher levels of cytotoxic IL-6. This suggests that in those who had the appropriate diversity of affinity at the location of infection - in this case, the lungs - were more successful at containing the viral infection. This reinforces the notion that a timely activation of the CD8+ T-cell response is critical to host defence.

The literature on TA-1 is not yet conclusive, but there is enough evidence to suggest that the benefits of $\alpha\beta$-Interferon and TA-1 should be investigated due to their synergistic effects in activating the adaptive arm of the immune system and activating resident immune cells, more adapted to the delicate environment of the lungs. The ultimate goal is to avoid damage-mediated recruitment, which seems to be present in severe COVID-19, as evidenced by the fibrotic changes in the lungs. $\alpha\beta$-interferon is known to augment the expression of antiviral interferon stimulated genes (ISGs), which have been observed to be modestly activated in a murine model of SARS-CoV infections [74].

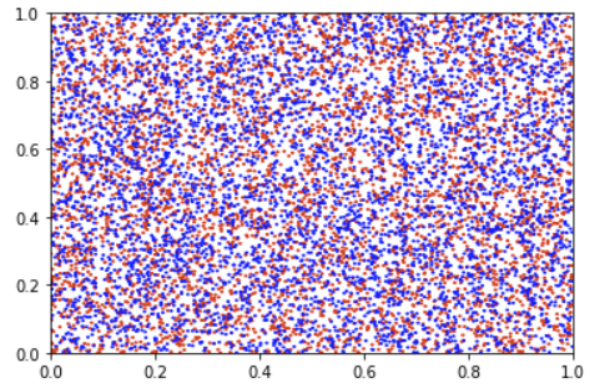

Figure 1: Schematic of young lymph node T-cell populations

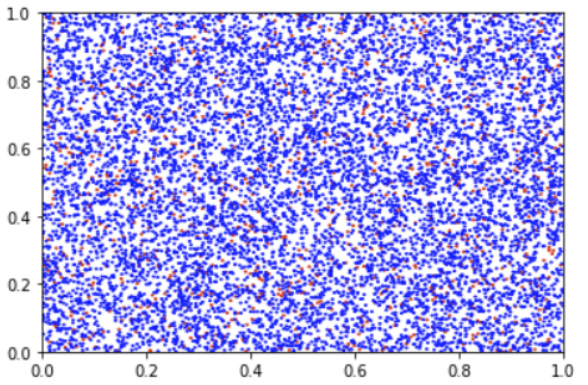

Figure 2: Schematic of elderly lymph node T-cell populations

Figure 2 shows a schematic of a geriatric and Figure 1, one of a pediatric population's lymph nodes. The red circles represent TREC cells whereas the blue cells represent cells that have undergone clonal proliferation.

This example illustrates the difference in diversity between the elderly and pediatric lymph nodes and clearly illustrates how a rare red cell might be made more difficult to find in an elderly patient. A delay in the presentation due to the rarity of clonotypes specific to the disease would result in clinical manifestations consistent with severe COVID-19.

Table 5 showed the disease severity of hospitalized patients in Canada, Figure 3 shows an exponential increase in probability of death with age for hospitalized patients in Canada. This exponential increase in susceptibility is consistent with an exponential decrease in thymic output [49] although direct comparison is not even attempted as a consequence of the clear multifactorial nature of disease susceptibility.

Figure 4 shows a log-linear relationship between TRECs in the blood and death by COVID-19. TREC data was obtained from a previous study that measured the TREC concentration per millilitre of whole blood [34]. This relationship supports the conclusion but does not confirm it as measurements of TREC proportions in infected cells have not been observed. It is clear that more work must be done to more precisely measure the mechanism by which this exchange between diversity and specificity affects disease susceptibility. It should be noted that in a recent paper which studied the efficacy of TA-1, that teams of healthcare workers had been given doses of Thymosin-α-1 before heading to Hubei as a prophylactic measure [31]. The hypothesis of the link between thymic output and disease severity had been put forward prior to the author's knowledge of the efficacy of TA-1 in treating COVID-19 patients, and therefore lends credibility to this hypothesis. While these hypotheses do in fact agree with all the known datasets of which the authors are aware, due to the pleiotropic effects of TA-1, this paper does not confirm the fact that diversity is the causal link. This hypothesis must be thoroughly investigated with the use of molecular-level high throughput techniques. The synergistic effects of TA-1 and $\alpha\beta$-Interferon intended to stimulate the adaptive response have been previously observed in enhancing NK activity, so this approach is not completely novel [18].

3.5 Viruses as a host-defence mechanism

It is impossible to study this topic without noticing the fact that viruses seem to be an evolved means of host defence at the species level against the threat of another species monopolizing limited resources. In a situation where there are frequent interactions between two species competing for the same resources, there is an increased risk, especially in the presence of a respiratory virus, that a mutation can occur that renders the other species susceptible to a disease which is well tolerated in the donor species. As a consequence, our virome, the set of viruses that we tolerate and can carry with us, can be interpreted as a means of defence against an invading species which threatens our survival and competes with us for available resources. In the receiving species, it is those members who, for a multitude of reasons, are better able to sustain diversity in their immune repertoire who are favoured to have a mild clinical course. As diversity decreases with age, this species-level transmission clearly favors the young and those who have maintained hormonal and immune homeostasis. Furthermore, by the mere fact that the virus is well tolerated, it is plausible that these viruses have evolved for a number of years, under selection pressure, to be less harmful and as such are a fitness test. This test measures the ability to mount an immune response in the presence of rarely seen antigenic molecular patterns. Those members of the

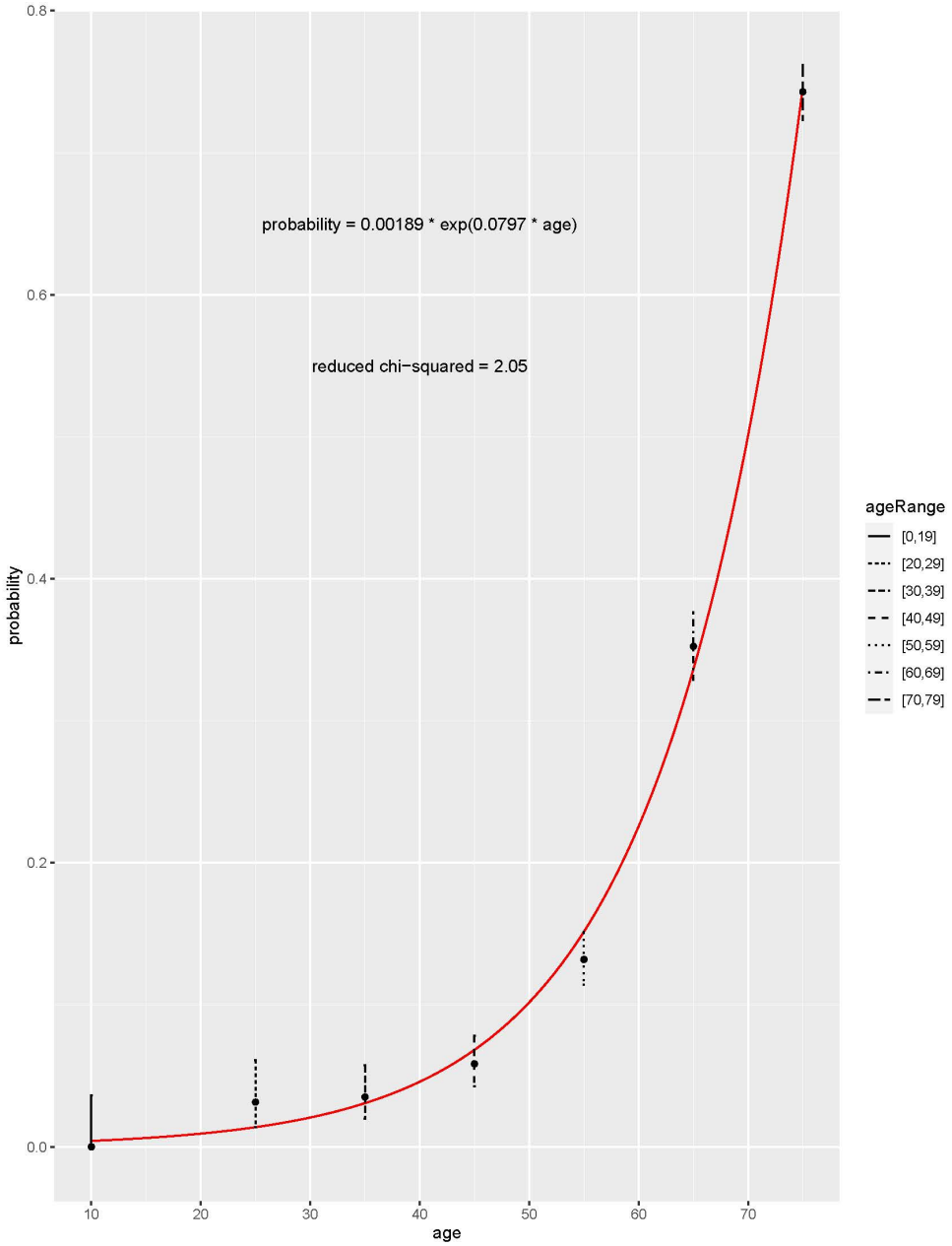

Figure 3: Probability of death conditional on hospitalization as a function of age, with a fitted exponential trend.

species, incapable of maintaining an adequate and sustained diversity in their immune reservoir are quite possibly at higher risk of developing severe COVID-19, something which seems to be supported by all known risk factors.

3.6 Aging

The connection between aging and susceptibility to COVID-19 infection is clearly shown in Figure 3. The link between aging and the thymus had been previously made [49], and it is the opinion of these authors that the thymic output is a crucial element of the aging process, and needs to be investigated thoroughly. While the bone marrow progenitors age as well, which essentially makes the T-cells less functional as they exit an aging thymus, it is clear that in combination with thymic rejuvenation, young stem cells may have the potential to better maintain a diverse and functional immune system. However, the nature of the selection process in the lymph nodes which favours specificity would need to be re-balanced in a way as to provide new thymic emigrants with the opportunity to make a meaningful contribution to this

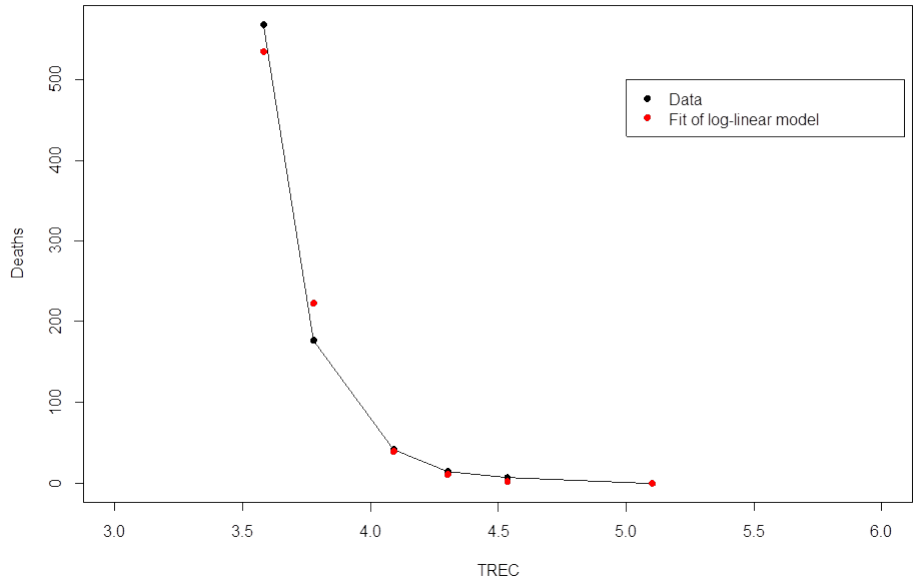

Figure 4: Average TREC concentration in the blood as a function of number of deaths, stratified by age.

	Hospitalizations			Admitted to ICU			Deceased		
Age groups	To June 1 (%)	2-8 June (%)	9-15 June (%)	To June 1 (%)	2-8 June (%)	9-15 June (%)	To June 1 (%)	2-8 June (%)	9-15 June (%)
≤ 19	1.0	2.1	2.0	1.0	2.6	0.0	0.0	0.0	0.0
20-29	2.6	3.8	2.0	3.7	5.3	0.0	0.1	0.0	0.0
30-39	4.4	5.1	5.2	4.6	0.0	15.8	0.2	0.0	0.0
40-49	7.5	6.4	7.8	9.8	10.5	21.1	0.5	0.0	0.0
50-59	13.8	14.9	16.3	20.4	15.8	15.8	2.2	0.0	8.2
60-69	16.8	18.3	12.4	25.0	23.7	26.3	6.9	9.5	6.1
70-79	20.8	17.9	20.9	24.0	26.3	15.8	18.1	19.0	10.2
80+	33.2	31.5	33.3	11.4	15.8	5.3	72.0	71.4	75.5
Gender									
Female	48.4	46.0	50.3	38.4	34.2	31.6	54.2	54.2	51.0
Male	51.6	54.0	49.7	61.6	65.8	68.4	45.8	45.8	49.0

Figure 5: Epidemiological summary of case severity from the beginning of the outbreak to June 17th, 2020. Source: Weekly Epidemiological Update (11-17 June, 2020), Public Health Agency of Canada (PHAC) [46]

reservoir. As is, the selection process means that the thymic output is a means of increasing the bioavailability of thymic diversity. However, it would be more effective if that diversity could be maintained in an aged lymph node. There is no clear solution to this problem for the moment. Furthermore the aging process, like many evolved biological processes, is extremely multifactorial. There is also an epigenetic component to it, which is likely to be a significant part of the lymph node "maturation" process. Links have been made between aging and autophagy, fasting, and epigenetic changes [45, 33]. We suggest that thymic reconstitution should be considered as a topic of investigation in the science of aging as it provides a constant stream of bioavailable and diverse T-cells that can respond to foreign antigenic molecular patterns, a phenomenon that is not exclusive to viral infections.

3.7 Alternative Hypotheses

3.7.1 Regulatory T-cells and self-antigens

An alternative hypothesis consistent with the data is that the viral epitopes may produce clonal expansions of self-reactive clonotypes of T-cells. Some self-reactive clonotypes are known to be suppressed by regulatory T-cells [57]. These clonotypes would not only be rare in abundance under normal conditions, but also be suppressed by regulatory T-cells which would also lead to a delay in the activation and clonal expansion leading to the lymphopenia observed. This hypothesis seems consistent with the instances of Kawasaki syndrome occurring in the pediatric population affected by COVID-19. Indeed, a clonal expansion of self-reactive T-cells would cause disseminated inflammation in the absence of virally infected cells.

3.7.2 ACE2 Expression

It has been suggested that variations in ACE2 expression could be a causal link which makes children less susceptible to COVID-19 infection. While it is true that children have fewer ACE2 receptors, the difference in expression is not significant enough to account for both the wide differences in susceptibility as well as the lymphopenia observed in the most severe clinical cases.

3.7.3 NK cells

Some Natural Killer (NK) cells are of thymic origin, and they are also thought to become less diverse in function with age. They may play a more dominant role in the initial cointainment of the viral inoculum in children [59, 60]. It could be that the increase in diversity and lack of maturation of NK cells in children is an asset in terms of SARS-CoV-2 susceptibility.

4 Conclusion

Further work needs to be done to elucidate the importance of thymic output to the long-term survival of the host, especially in the presence of an infection such as COVID-19. There has been some shift in the recognition of the importance of the thymus as individuals age, particularly in terms of its ability to preserve the immune response to novel antigenic fitness challenges such as certain cancers [49]. Aging results in the development of a biased distribution of T-cell receptors in the periphery, and as such, the successful presentation to an unused and rare clonotype is delayed on average. In the case of a zoonotic transmission, not only has there been selection pressure in the donor species, rendering the disease less harmful, but the fact that the virus has not co-evolved with the receiving species may contribute to the lack of efficient response.

The efficacy of thymosin-α-1-Fc (TA-1) in a recent clinical trial [31] may have been through the facilitation of presentation of antigens to rare T-cell clonotypes. The oligoclonal nature of the diversity in the aging lymph nodes and the low amounts of naive thymic T-cells produced relative to those maintained by recurrent viral infections such as Cytomegalovirus (CMV) has been suggested as one cause of this lack of diversity [27]. Furthermore, it is established science that the immune system becomes senescent in the elderly population and is less capable of mounting a vigorous response to novel viral challenges.

The availability in the blood of thymic emigrants is enhanced in a situation of lymphopenia where the relative abundance of thymic emigrants would be higher, which would in turn enhance the efficacy of TA-1 in a situation where there is a lack of diversity in the host response. In addition, a novel pandemic requires multiple points of investigation including non-pharmacological ones such as contact tracing [71, 70, 3], public health and epidemiological work as well as drug discovery [37], including both traditional methods and machine learning.

Author contributions

MR proposed the original idea of associating thymic output with SARS-COV-2 outcomes, wrote the paper and carried out the literature-based research. LC contributed to the data analysis of COVID-19 statistics and model inference. GA contributed to the literature review and provided a clinical perspective. LH and RT contributed to the literature review and framing of the discussion. DS contributed to the analysis of TREC and susceptibility datasets and model inference. IR contributed to critical discussions. All the authors participated in writing or editing the manuscript and approved its final version.

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