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Gene expression pattern in severely progressing covid-19 patients is related to diabetes mellitus type 1: A functional annotation analysis

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ABSTRACT

Aims: The aim of this study was to extract the signaling mediators or biological pathways that link covid-19 to other diseases such as type 1 diabetes mellitus (T1DM).
Methods: Microarray data of covid-19 (GSE164805) was extracted from Gene Expression Omnibus (GEO) and analyses were performed by R package and GEO2R. Functional enrichment analysis was done to extract enriched molecular pathways (MP), biological process (BP) and molecular function (MF). Then commonly up- and down-regulated genes in covid-19 and T1DM were extracted by comparing deferentially expressed genes (DEGs) of GSE164805 and GSE9006.
Results: Down-regulated DEGs in the severely progressing covid-19 patients (SPCP) had a link to T1DM. Major histocompatibility system (MHC) class II, gamma interferon (IFNγ), and IL-1B were enriched in extracted pathway that leads to T1DM. In addition, comparing extracted DEGs from GSE164805 and GSE9006 indicated that MTUS1, EGR1 and EGR3 are the genes that are up-regulated in both SPCP and T1DM.
Conclusion: The findings of this study indicate that coincidence of SARS-COV-2 infection and T1DM may increase the severity of both diseases. Although covid-19 reduced the T cell mediated immune response, but increased mediators of T-cell signaling pathway such as IL-1 in both diseases. This could potentiate the inflammation response and worsens the severity of covid-19 cytokine storm or increase the resistance to insulin.

1. Introduction

On 12 December 2019, a new type of coronavirus was reported in Wuhan, Hubei province, in China (Cheng and Shan, 2020). On 11 February 2020, a new name was announced by World Health Organization (WHO) for the epidemic disease caused by 2019-novel coronavirus (2019-nCoV): coronavirus disease (COVID-19) (Gorbalenya et al., 2020). The 2019-novel coronavirus was classified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) by the International Committee on Taxonomy of Viruses (del Rio and Malani, 2020).

Coronaviruses discovered in 1960s are the largest family of the RNA viruses and their genomes range from 27 to 32 kb in size. Covid-19 which is a member of this family is a single-stranded enveloped RNA virus with a positive-sense RNA genome (+ssRNA) (Kahn and McIntosh, 2005). Coronaviruses have few common characteristics that are applicable to covid-19 as well.

Symptoms of covid-19 range from minimal symptoms to severe respiratory failure. The prevalent symptoms are fever, cough, shortness of breath, leukopenia, and pneumonia in both lungs (Greenberg, 2016). However, there may be positive cases without symptoms. WHO dashboard shows that as of 11 August, there have been 205,338,159 confirmed cases of covid-19, including 4,333,094 deaths (https://covid19.who.int/?gclid=EAIaIQobChMIpOr4qoWz8gIVSvSzCh3kKQUIEAAYASABEgIDq_D_BwE).

At the beginning of the outbreak, it was thought that covid-19 is mainly associated with the elderly, but now there are reports of the disease among younger people and even children. (Yuki et al., 2020).

Some studies indicate that patients with underlying disease such as diabetes mellitus may be more prone to covid-19 (Bode et al., 2020; Chen et al., 2020; Zhu et al., 2020; Petrilli et al., 2020). Although many studies have been done on the relation of diabetes mellitus type 2 (T2DM) and covid-19, however limited studies are available on the

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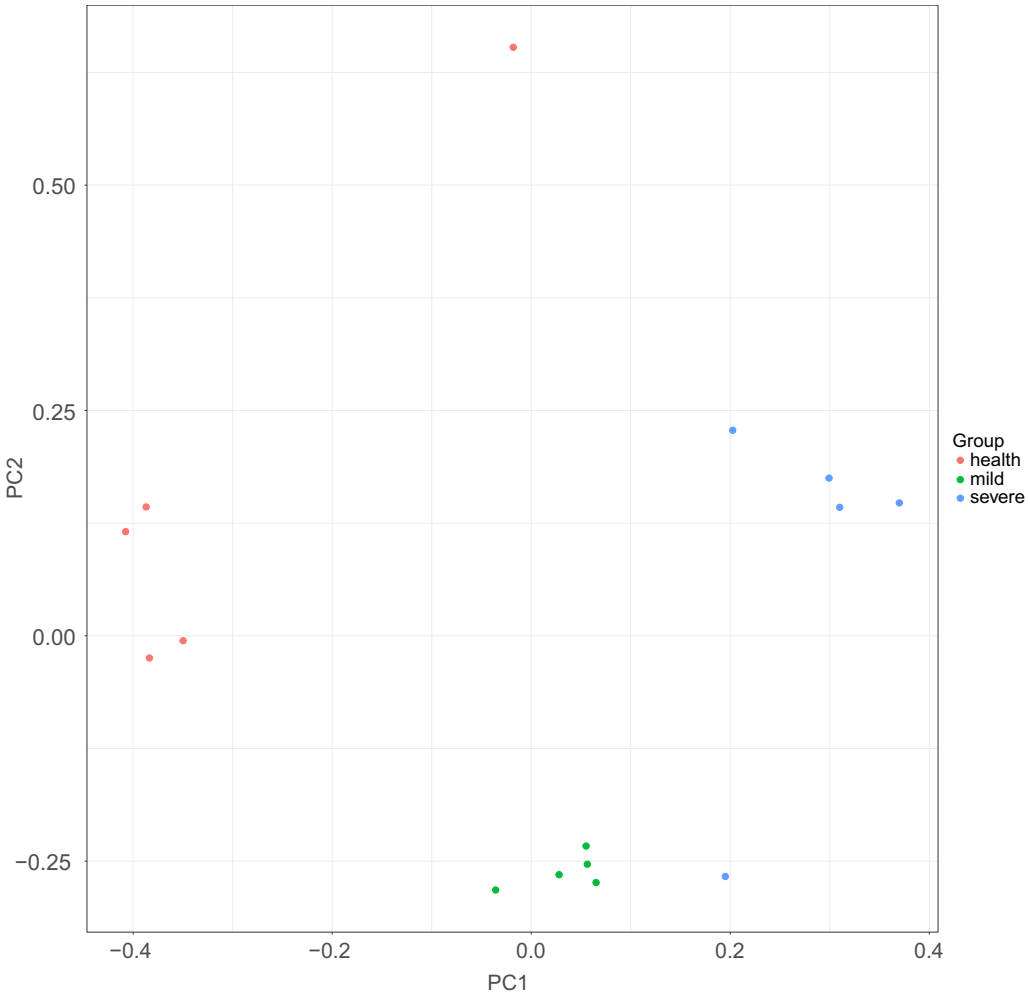

Fig. 1. Principal component analysis of GSE164805 microarray library showed that healthy, mild and severe groups were completely separated.

mechanisms linking covid-19 to T1DM.

There are a lot of epidemiological studies indicating T1DM as an immune-mediated disease. Other studies indicated that the pathways linking covid-19 to T1DM are related to regulation of immune system (Lim et al., 2021).

Although T1DM is considered as an autoimmune disease, yet other factors such as viruses and environmental factors have been suggested to induce immune system against beta-cell antigens through two mechanisms; direct cytotoxic effect on beta-cells and/or excitation of immune system against beta-cell antigens (Saberzadeh-Ardestani et al., 2018).

A nationwide study in England on 61,414,470 individuals showed that 263,830 (0•4%) of subjects, suffered from T1DM. From these subjects 364 (1.5%) deaths occurred among in-hospital T1DM patients which were due to infection with covid-19 (Barron et al., 2020).

Recently microarray data on covid-19 is increasing in Gene Expression Omnibus (GEO), a suitable repository of data to uncover the probable relation of covid-19 to other diseases. In addition, functional annotation analysis is a good tool that could increase our knowledge of the relation of covid-19 to other diseases. So the aims of the study were to evaluate the change in gene expression profile in covid-19 infection to extract deferential expressed genes (DEGs); to observe them at the level of biological process (BP), cellular components (CC) and molecular functions (MF); and to examine if there is a relation between covid-19 and other diseases such as T1DM.

2. Methods

2.1. Data extraction and analysis

Microarray data, GSE164805, was extracted from GEO library. The study participants in GSE164805 were 5 healthy subjects, 5 severely progressing covid-19 patients (SPCP) and 5 mild progressing covid-19 patients (MPCP). This data series was selected because it was one of the first microarray libraries presented on GEO which studied mild and severely progressing covid-19 patients in comparison to healthy subjects. Analysis and normalization of data were done by GEO2R and R package (version 4.1.0). Conversion of data to log2 fold change (log2 FC) was performed by R package. Principal component analysis (PCA) used to survey the quality of data and correlation of the genes and samples. PCA was performed to reduce dimensionality without losing much of data. This was down by discarding the component with low information and considering the remaining components. To prevent domination of variable over other variables standardization was performed. Functional annotation and enrichment analysis was performed by Enrichr (August 9, 2021), the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 and PANTHER 16. Gene ontology (GO) was investigated based on BP, CC and MF. The enriched pathways were surveyed by Kyoto Encyclopedia for Genes and Genomes (KEGG).

First, DEGs in the range of $-1 > \text{Log2FC} > 1$ were extracted for MPCP and SPCP, and functional enrichment analysis was performed. However, none of the data were statistically significant in the annotation analysis.

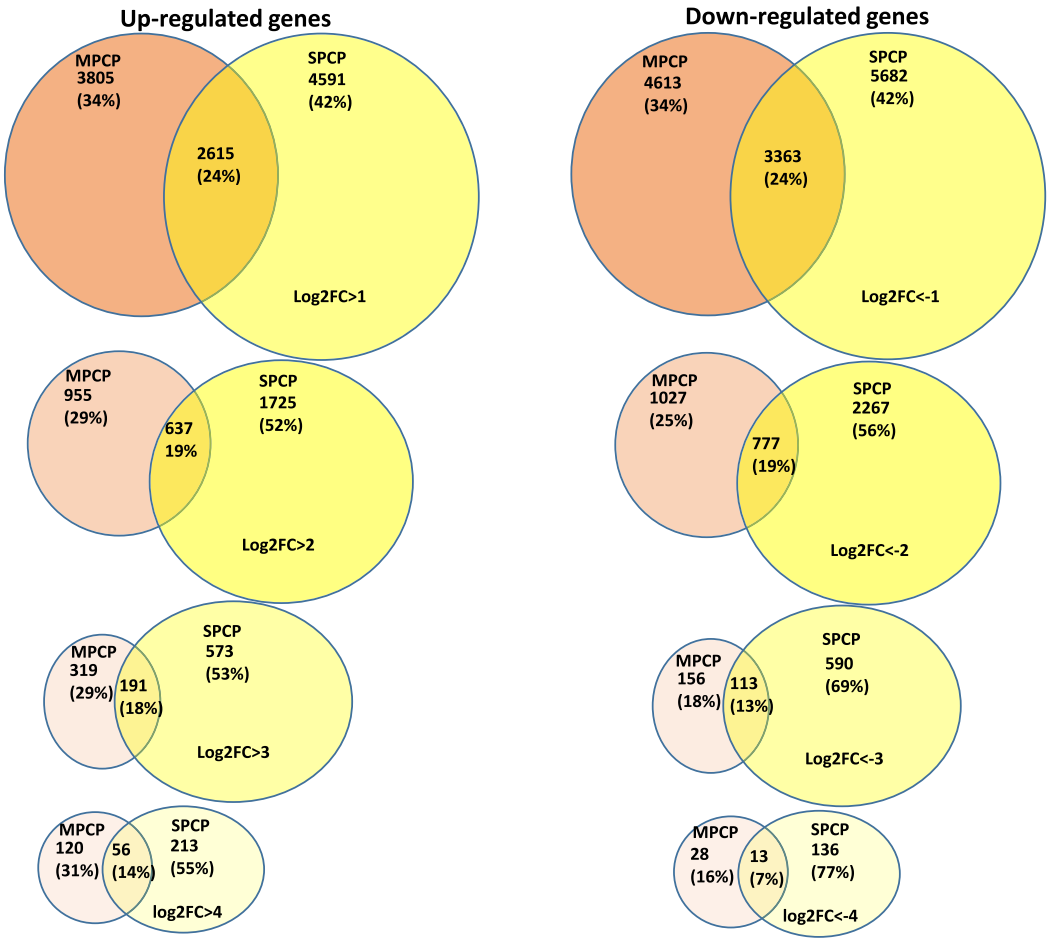

Fig. 2. Up- and down-regulated genes in mild and severely progressing covid-19 patients.
This figure shows the number of genes that specifically up-regulated or down-regulated in MPCP and SPCP. Also the genes that are commonly up- or down-regulated in MPCP and SPCP are illustrated. Up-regulate genes, down regulated genes and common genes were extracted in eight level of log2 FC as shown in the figure. All the genes that were extracted had adjusted p-value<0.05. Note: MPCP: mild progressing covid-19 patients; SPCP: severe progressing covid-19 patients.

Thus, in the next step, DEGs with Log2FC > 2, 3 and 4 and log2FC < −2, −3 and − 4 were extracted. In each step, after extraction of the DEGs, enrichment analysis was performed. Only the DEGs extracted in log2FC < −3 for SPCP showed a statistically significant results in annotation analysis, so we confined our analysis to these DEGs. Since analysis showed that the DEGs are related to other disease such as T1DM, so the microarray data GSE9006 was extracted from GEO library because the library was composed of 24 healthy subjects and 43 newly diagnosed T1DM patients and the cells used in the study were similar to GSE164805. Then normalization and conversion of data to log2 FC were done by R package. DEGs in the range of -1 > Log2 FC > 1 were extracted and compared to corresponding DEGs in SPCP. Commonly up- and down-regulated genes between MPCP and SPCP, and between SPCP and T1DM were extracted by Venny 2.1 (Venny, 2007-2015).

2.2. Statistical analysis

Analysis was performed by GEO2R and R package. Adjusted *p* value <0.05 or p value less than 0.01 was considered to be significant.

3. Results

3.1. Principal component analysis

We found that PCA completely separated the healthy, MPCP and SPCP of GSE164805 library (Fig. 1). Only a sample in SPCP was close to the MPCP group, albeit there was no overlap. In addition, pheatmap showed that the groups were separated as a cluster (Supplementary Fig. 1). The largest amount of variance was seen in PC1 and PC2 (data note shown).

Table 1
Up- and down-regulated genes in T1DM.

Up-regulated genes		
Gene symbol	Log2FC > 1	Adjusted p-value
ZNF79	1.0081702	0.0305323
MTUS1	1.0095114	0.0243145
PRG3	1.0734726	0.0305323
EGR1	1.0762533	0.0342742
EGR3	1.1352496	0.0061521
ADAMTS20	1.144175	0.0143093
IL1B	1.3669317	0.002109
IGLC1	1.5300166	0.0200435
FOSB	2.1290828	0.0276746
EGR2	2.1374702	0.0000375
HLA-DRB4	3.5025114	0.0093727
Down-regulated genes		
Gene symbol	Log2FC < −1	Adjusted P Value
KIAA0319L	−1.2394676	0.0148668

This Table shows the genes that up-regulated or down-regulated in T1DM. Gene symbols are tabulated. Up- and down-regulated genes were extracted on the −1 > log2 FC > 1. All the genes that were extracted had adjusted p-value <0.05.

Table 2
Transcription factors protein-protein interaction for severely progressing covid-19 gene set.

Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	ILF3	0.00002681	0.004076	2.83	29.82
2	RAD21	0.001875	0.1425	2.42	15.20
3	UPF1	0.008436	0.4274	2.95	14.09
4	ERG	0.03209	0.6097	3.57	12.29
5	RFX5	0.08826	0.9313	4.40	10.68
6	E2F2	0.05755	0.7952	3.67	10.48
7	TAF1	0.01278	0.4855	2.29	9.97
8	PLAGL2	0.1891	0.9736	5.49	9.14
9	MAFK	0.1068	0.9313	3.88	8.68
10	ILF2	0.02091	0.5234	2.11	8.17

Ten top PPIs that had the least adjusted p-value, and the highest odds ratio and combined score were tabulated for severely progressing covid-19 gene set. DEGs that used for extraction of PPI were down-regulated genes with log 2 FC < -3. This table indicates that ILF3 with a statistically significant adjusted *p*-value is related to down-regulated gene set.

3.2. Deferentially expressed genes (DEGs)

We summarized the number and percent of up-regulated, down-regulated and commonly up- and down-regulated genes for MPCP and SPCP in Fig. 2. Gene symbols are summarized in supplementary Table 1. In MPCP, 3805,955,319, and 120 genes were up-regulated respectively with log2FC >1, log2FC >2, log2FC >3 and log2FC >4. Similarly, for SPCP 4591, 1725, 573, and 213 genes were up-regulated that were associated respectively with log2FC >1, log2FC >2, log2FC >3 and log2FC >4. On the other hand, 4613, 1027,156 and 28 down-regulated genes in MPCP were associated with log2FC < −1, log2FC < −2, log2FC < −3 and log2FC < −4, respectively. In SPCP 5682, 2267, 590, and 136 down-regulated genes were associated with log2FC < −1, log2FC < −2, log2FC < −3, and log2FC < −4, respectively. Up- and down-regulated genes for T1DM are summarized in Table 1. Analysis showed that 11 genes were up-regulated with log2FC > 1 and one gene was down-regulated with log2FC < −1.

3.3. Functional enrichment analysis

Our findings showed that only DEGs with log2FC < −3 in SPCP (590 DEGs) had statistically significant results in annotation studies. Transcription factor protein-protein interaction (PPI) is summarized in Table 2. Interleukin enhancer-binding factor 3 (ILF3) had the highest score which affects RPL5, NDUFB9, MRPS35, RPL22, NUCKS1, RPAP1, MRPL41, YY1, RPL7A, RPS17, SFPQ, RPS16, SARS2, RPL18A, RPS3, LNX1, RPL13, PPT2, RPS2, HNRNPA1, NDUFV1, and EIF2A as target genes. hsa-miR-3180-5p (P = 0.003472; target genes: AQR, IMMP2L, RPL18A, STARD7, UBR7, PLCG1, RASGRP1, CD3D, ATF3, TRABD2A, CEP78) and has-miR-6866-3p (P = 0.006605; target genes: RAB4A, MTRNR2L10, UBR7, ADORA3, CLDN12, PLCG1, CD44, SLC7A2) were the most important ones that enriched in human cells.

We found 80 BP terms for down-regulated genes. Ten top BPs which had the least and significant *p* values are depicted in Fig. 3. Translational initiation (adj.p.val = 3.5E-11), SRP-dependent translational protein targeting to membrane (adj.p.val = 4.5E-10), nuclear-transcribed mRNA catabolic process (adj.p.val = 4.5E-10), translation(4.5E-10 = 7.0E-9), viral transcription(4.5E-10 = 7.0E-9), antigen processing and presentation of peptide or polysaccharide antigen via MHC class II (7.0E-9 = 2.1E-5) and rRNA processing (adj.p.val = 2.1E-5) were the top BPs.

Molecular function terms including structural constituent of ribosome, poly(A) RNA binding, MHC class II receptor activity, RNA binding, MHC class II protein complex binding are summarized in Fig. 4. Moreover, 30 cellular component terms were extracted. 6 terms which had significant *p* values are depicted in Fig. 5. Ribosome, cytosolic large and small ribosomal subunits, cytosolic small ribosomal subunit, MHC class II protein complex, membrane and lysosome are illustrated in Fig. 5.

Ten top diseases extracted by KEGG and had the least significant p values are summarized in Table 3. One of the diseases with a high score linking to this gene set, is T1DM. The common pathway between T1DM and covid-19 is depicted in Fig. 6. The genes that enriched in pathway for T1DM were MHC class II, INFγ and IL-1.

We extracted DEGs for GSE9006. Results showed that 11 genes were up-regulated with log2FC > 1 and one gene was down-regulated with log2FC < −1. There was no gene that commonly down-regulated in T1DM and severe covid-19 with log2FC < −1. However, venny analysis based on the two microarray analysis extracted three genes that commonly up-regulated in T1DM and SPCP with log2FC > 1 including MTUS1, EGR1 and EGR3.

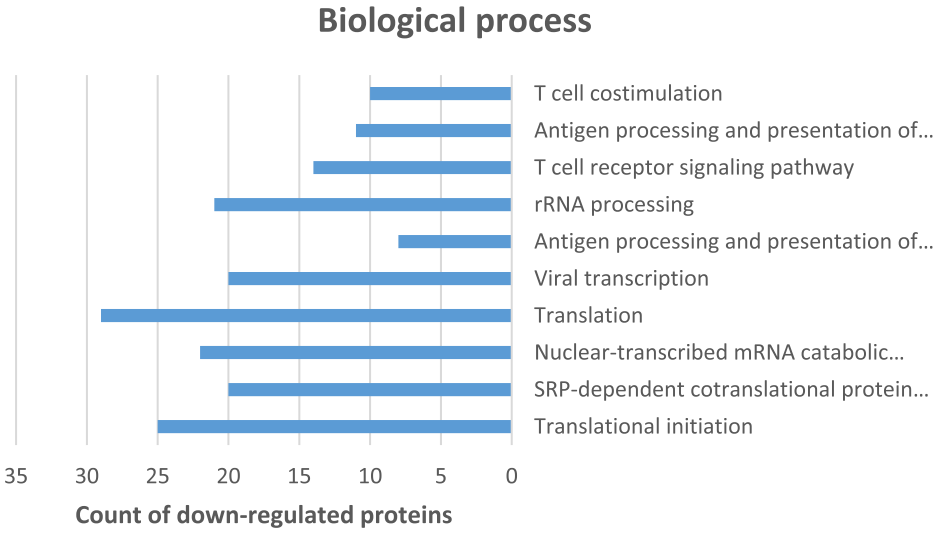

Fig. 3. Biological process (BP) associated with severely progressing covid-19 gene set.
Ten top BPs that had the least p-value were illustrated for severe covid-19 gene set. DEGs that used for extraction of BPs were down-regulated genes with log 2 FC < -3.

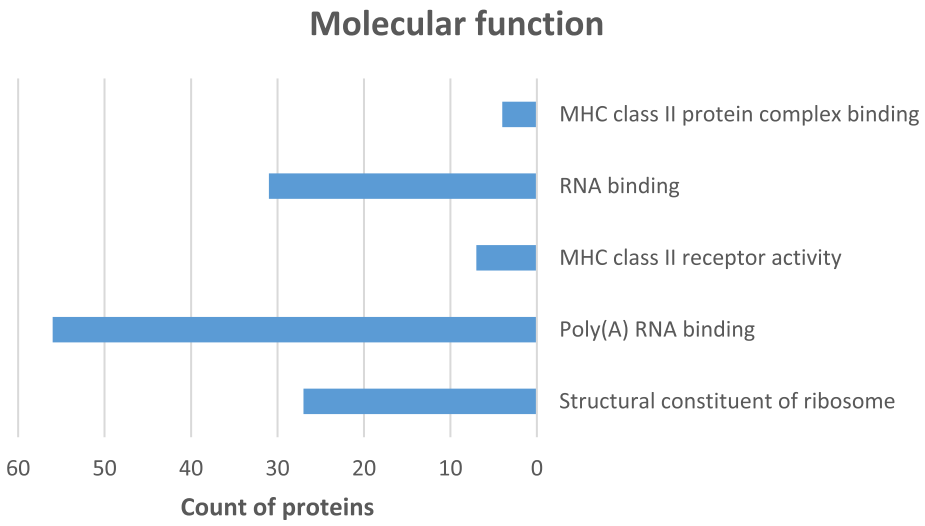

Fig. 4. Molecular functions (MF) associated with severely progressing covid-19 gene set.
Five top MFs that had the least and significant p-value were illustrated for severe covid-19 gene set. DEGs that used for extraction of MFs were down-regulated genes with log 2 FC < -3.

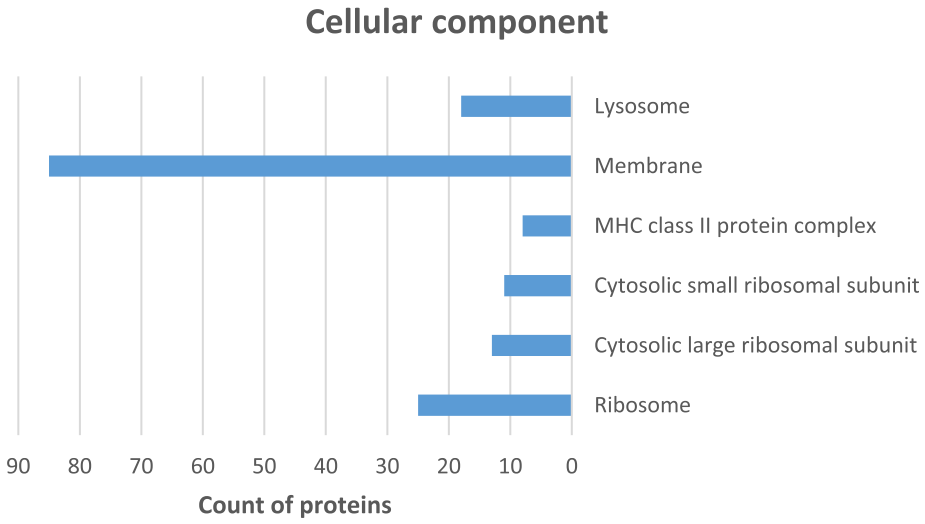

Fig. 5. Cellular components (CC) for severely progressing covid-19 gene set.
Top CCs that had the least and significant p-value were illustrated for severe covid-19 gene set. DEGs that used for extraction of CC were down-regulated genes with log 2 FC < -3.

4. Discussion

The main finding of our study was that statistically significant results in functional annotation analysis were only found for DEGs with log2FC < -3 in SPCP. Some studies declared the association of covid-19 mortality with T1DM and T2DM (Barron et al., 2020). Pathway analysis by KEGG revealed that T1DM is one of the diseases linked to DEGs in SPCP. Little is known about the interplay of immune system with covid-19. It is believed that genetic and environmental factors such as viruses could trigger an immune response against beta-cells of pancreas (Torpy et al., 2007).

In transcription factor PPI, our analysis showed that ILF3 had the highest combined score and significant adjusted *p*-value. ILF3 is a dsRNA binding protein which is required for translation of an antiviral cytokine, INFB1. Samir et.al study indicated that ILF3 has a key role in expression of antiviral defense mRNA (Watson et al., 2020). Watson group claimed that this phenotype of immune system is associated with T2DM which make these patients more prone to covid-19 (Alzaid et al., 2020).

BP, CC and MF analysis showed that MHC class II and presentation of peptide or polysaccharide antigen via MHC class II is one of the most important factors that may be affected in SPCP. Covid-19 inhibits cell-mediated immune response through down-regulation of MHC class I and II, and consequently antigen presentation (Paces et al., 2020). Zhang group showed myeloid cells over activation and deficiency of T cell function in covid-19 patients (Zhang et al., 2021). However, our microarray and pathway analysis indicated that T-cell receptor signaling pathway through INFγ and IL-1 can increase the inflammation and initiate the apoptosis in beta-cells.

Our analysis on GSE9006 showed that pro-inflammatory cytokine IL-1B is up-regulated in T1DM. IL-1B is an important factor for local and systemic inflammation due to viral infection. In addition it triggers lung and tissue inflammation, and causes fever and fibrosis (Kritas et al., 2020). Previous studies indicated that covid-19 binds to Toll Like Receptor (TLR) and induces production of pro-inflammatory cytokines including IL-1. Blocking of IL-1 receptors has been suggested as a

Table 3
KEGG pathway analysis for severely progressing covid-19 gene set.

Index	Name	P-value	Adjusted p-value	Odds ratio	Combined score
1	Graft-versus-host disease	0.000002974	0.0001387	9.10	115.75
2	Ribosome	1.568e-9	4.156e-7	5.49	111.28
3	Type 1 diabetes mellitus	0.000003664	0.0001387	8.83	110.50
4	Asthma	0.00002663	0.0005881	9.70	102.16
5	Allograft rejection	0.00001224	0.0003604	8.88	100.44
6	Th1 and Th2 cell differentiation	4.918e-7	0.00003814	6.02	87.50
7	Th17 cell differentiation	5.757e-7	0.0003814	5.48	78.70
8	Viral myocarditis	0.000009238	0.0003060	6.68	77.39
9	Coronavirus disease	2.590e-8	0.000003432	4.10	71.71
10	Rheumatoid arthritis	0.000003356	0.0001387	5.44	68.62

Ten top diseases that had the least adjusted p-value and the highest odds ratio and combined score were tabulated for severely progressing covid-19 gene set. DEGs that used for extraction of disease by KEGG were down-regulated genes with log 2 FC < -3. This table indicates that type 1 diabetes mellitus is related to down-regulated gene set.

treatment procedure to prevent cytokine storm (Lian et al., 2020). Now the question is that whether the manifestation of covid-19 such as inflammation is more severe in T1DM or not. Although MHC II is down-regulated in covid-19 patients, but mediators of signal transduction through MHC II may up-regulated in both covid-19 and T1DM.

MTUS1, EGR1 and EGR3 are the up-regulated genes in T1DM and covid-19. Numerous targeted genes are regulated by early growth response protein 1(EGR1), so that it has an important role in regulating the response to growth factors, DNA damage, ischemia and hypoxia. It regulates the expression of proteins such as IL1B and CXCL2 that are involved in inflammatory processes and development of tissue damage after ischemia (https://www.uniprot.org/uniprot/P18146). Lungs are involved in hypoxia and dyspnea that manifest in severely progressing covid-19 (Kashani, 2020). Tsugata group claimed that up-regulation of Egr1 gene in human-induced pluripotent stem cells (iPSCs) suppresses differentiation of these cells into pancreatic endoderm and insulin-producing cells (Tsugata et al., 2018).

EGR3 has a role in regulation of gamma-delta T cell differentiation (https://www.uniprot.org/uniprot/Q06889). Our body in some situation like infection with a pathogen, increases γδ T cells a few days after infection. In addition, these cells could stimulate the secretion of IFNγ. (Li et al., 2013; Xue et al., 2017). Some studies indicated that IFNγ is a risk factor for mortality of covid-19 (Gadotti et al., 2020). Silvia group showed that $CD8^+$ T cells have a strong reaction against preproinsulin (PPI) peptides through IFNγ (Rathmann et al., 2004). IFNγ considered being a key factor in cytokine release storm (CRS). It is a proinflammatory cytokine produced by T-cells and NK-cells. It induces macrophages to release TNFa, IL1b, IL6, IL8, and IL10. This processes help to

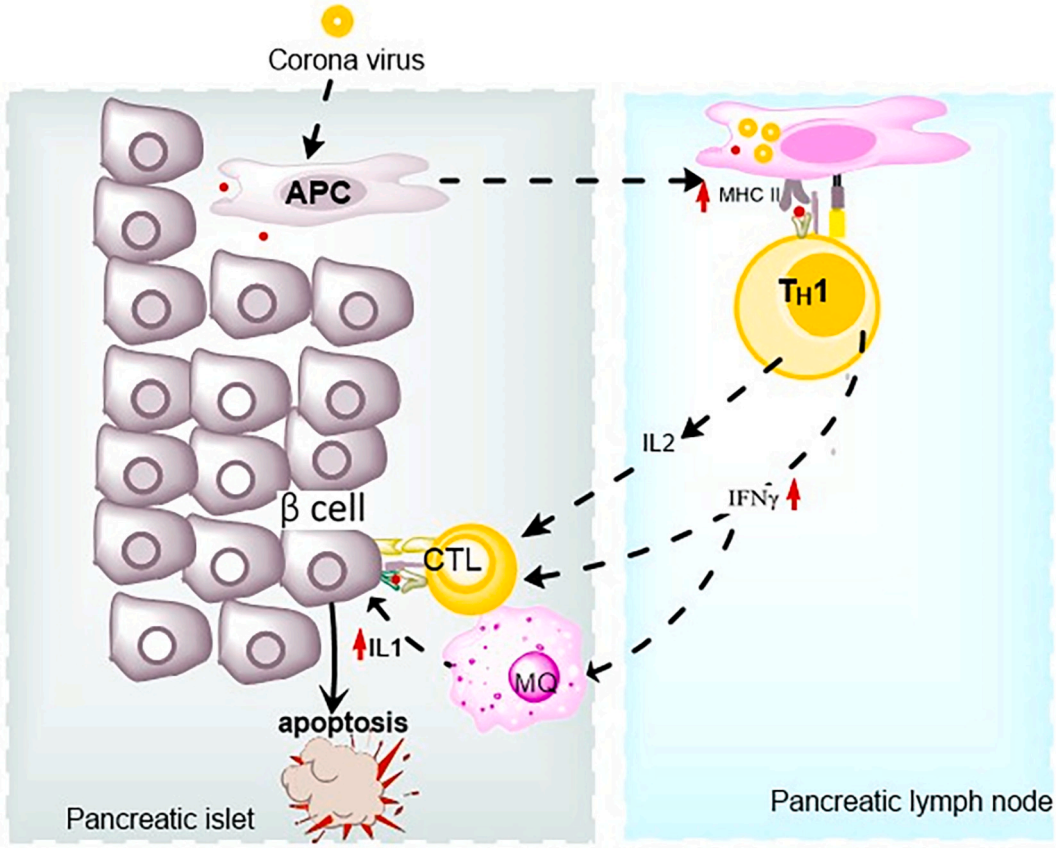

Fig. 6. KEGG pathway output base on the severely progressing covid-19 gene set. Proteins highlighted with red arrow were enriched.
Corona virus interplays with APC and is presented to TH1 through MHC II. IFNγ secreted by TH1 stimulates MQ and CTL which trigger the apoptosis cascade in β-cells by secreting IL-1 and interaction with Fas, respectively. Notes: APC: Antigen presenting cell; CTL: Cytotoxic $CD8^+$ T Cell; IL-2: Interleukin 2; IFNγ: Interferon γ; MQ: macrophage; MHC II: Major histocompatibility complex II; TH1: T helper I. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a cascade that lead to CRS (Yildizhan and Kaynar, 2018). It has been reported that cytokine storm may contribute to pathogenesis of covid-19 specially in those who are severely ill (Moore and June, 2020). Serum level of some cytokines including interleukin-1β, interleukin-6, IP-10, TNF, interferon-γ are elevated in covid-19 and are associated with cytokine storm (Huang et al., 2020). Kevin group showed that IFNγ increased the expression of co-inhibitory receptor programmed death-1 (PD-1) in T1DM which is correlated with insulitis (Osum et al., 2018). Taking together, these findings indicated that IFNγ is a risk factor for severity of covid-19 and T1DM.

Some mechanisms have been reported that link the inflammation to insulin resistance (Šestan et al., 2018). The massive inflammation response in covid-19 can impair the function of liver and skeletal muscles which are the major organs that are responsible for uptaking glucose in response to insulin (Groop et al., 1989). In addition, severely progressing covid-19 causes muscle weakness and elevation of liver enzyme activities, which might suggest multiple organ failure, particularly during CRS (Groop et al., 1989).

Therefore, based on the results it seems that T1DM patients infected with covid-19 may have a weaker response to insulin due to synergistic effect of increasing inflammatory factors such as IL-1B and IFNγ, and overexpression of EGR1. Animal studies have revealed that IL-1B is a key factor that could suppress metabolic health (Stienstra et al., 2010). This concept is supported by the findings that mice lacked one of the components of inflammasome such as IL-1B or its receptor was protected against insulin resistance (Spranger et al., 2003; Stienstra et al., 2012; McGillicuddy et al., 2011).

Some studies indicated that laboratory findings differ in covid-19 patients and depend on underlying cause. Plasma concentration of IFNγ and IL-1B has different levels in cytokine storm due to CAR T-cell therapy and systemic infection (Fajgenbaum and June, 2020). Therefore, our finding indicated that measurement of plasma IFNγ and IL-1B besides other laboratory findings including cell blood count, D-dimer level, inflammatory acute phase biomarkers and clinical features in SPCP with T1DM could be used as a prognostic factor. Also it may help to select the best therapy for these patients and to decide whether use immunosuppressive treatments or not. Since our finding indicated that T1DM patients infected with covid-19 may show resistance to insulin so we suggest that the dosage of insulin for these patients may need to be optimized again.

5. Conclusion

The findings of this study indicate that coincidence of covid-19 infection and T1DM may increase the severity of both the diseases. Although covid-19 induced reduction of the T cell mediated immune response, increasing mediators of T-cell signaling pathway such as Il-1 and IFNγ in both diseases could compensate the inflammation response and worsen the severity of covid-19 cytokine storm or increase the resistance to insulin. The limitation of the study was that we didn't find microarray data library that investigated DEGs in T1DM patients infected with covid-19. Thus our findings should be interpreted with caution.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

CRediT authorship contribution statement

Mohsen Alipour: Visualization, Software, Investigation, Writing – review & editing. **Danesh Javeshghani:** Writing – original draft, Writing – review & editing. **Abazar Roustazadeh:** Supervision, Conceptualization, Methodology, Software.

Declaration of Competing Interest

None for all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humgen.2022.201039.

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NovoNordisk. H.-S.K. has been a member of advisory boards or has consulted with Pfizer, Boehringer Ingelheim, Novartis, Daewoong Pharmaceutical, JW Pharmaceutical and NovoNordisk. H.-S.K. has received grant support from AstraZeneca. H.-S.K. has also served on the speakers' bureau of Eli Lilly & Co., Merck, Sharp & Dohme, YUHAN, Dong-A Pharmaceutical and NovoNordisk. M.A.N. has been a member of advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Fractyl, GlaxoSmithKline, Menarini/Berlin-Chemie, Merck, Sharp & Dohme and NovoNordisk. M.A.N. has received grant support from AstraZeneca, Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, Novartis Pharma and NovoNordisk. M.A.N. has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, NovoNordisk and Sun Pharma. J.H.B. declares no competing interests. Epub 2020/11/15.eng.

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