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Original article

Survivin: A key apoptosis inhibitor in COVID-19 infection and its implication for treatment protocol

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ABSTRACT

While the relationship between cellular apoptosis and proliferation rates in COVID patients remains underexplored in existing literature, various viruses are known to impact these fundamental process to modulate response to infection. This paper aims to assess apoptosis and proliferation rates in individuals recently infected with Coronavirus, both before and after vaccination, comparing them with healthy controls. Peripheral blood cells from newly diagnosed COVID-19 patients revealed a significant increase in proliferation and apoptosis levels in fresh lymphocytes and granulocytes compared to healthy donors. Notably, as none of the patients were under corticosteroid therapy or cytotoxic drugs, the study underscores the critical role of white blood (WBC) apoptosis in viral pathogenesis, potentially contributing significantly to COVID-19′s pathogenicity. Elevated levels of soluble Fas ligand (FaSL) and the pro-inflatmmatory cytokine IL-38 were identified in COVID-19 patients, indicating potential immune dysregulation. Furthermore, individual who received the vaccine or recovered from COVID-19 exhibited higher survivin rates, suggesting a protective role for survivin in migitating lung damage. These findings suggest the prospect of developing a strategy to prevent WBC apoptosis, offering potential benefits in averting lymphopenia associated with severe COVID-19 ouctomes.

1. Introduction

SARS-CoV-2, the virus that causes COVID-19, is a pandemic virus currently affecting almost every country in the world. Due to its ability to mutate, there are worldwide concerns about its rapid spread with a consequential impact on mortality rates. However, after the development by many pharmaceutical companies of a range of vaccines, these rates have recently declined dramatically (Bandar et al., 2021; BinShaya et al., 2020). Apoptosis represents a crucial process that maintains cellular homeostasis and removes aged and damaged cells. Viruses (just like other microbes including bacteria and fungi) can invade cells and kill the infected host cells (Alenzi FQ, 2005). Once viral infection is initiated, apoptosis may offer a mechanism for proactively inducing rapid cell death, preventing a potentially lethal virus from spreading to other cells. In turn, other microbes may prevent active cell death to improve their survival and ability to replicate (Alenzi et al., 2014). There are at least four examples where apoptosis is tightly linked to viral infection—hepatitis C virus(HCV) (Fischer et al., 2007), reoviruses (Clarke et al., 2003), Severe acute respiratory syndrome (SARS)(Zhang et al., 2003), and human immunodeficiency virus)(HIV) (Sabri et al., 2003; Zauli et al., 1995). Cytokines and chemokines offer a key immunological link between dendritic cells (DC) and the various pathologies patients may present with. In inflammation, IL-38 is produced by apoptotic cells as a pro-inflammatory cytokine (Mora et al., 2016; Boutet et al., 2017). Despite the fundamental role of apoptosis, there is a paucity of literature explaining the relationship between apoptosis and proliferation rates in COVID-19 patients. The main aim of the study is to bridge this existing gap by assessing the indices of apoptosis and proliferation rates in individuals recently infected with SARS-CoV-2, both before and after vaccination. By doing so, the paper aim to unravel the intricate dynamics between viral infection, cellular responses, and potential therapeutic implications. This paper is essential to enhance understanding of COVID-19 pathogenesis and provide a foundation for targeted therapeutic strategies aimed at modulating apoptosis and proliferation rates. In essence, this paper endeavours to contribute novel insight that go beyond the current knowledge landscape, fostering advancement in both basic and clinical science to better combat the challenges posed by COVID-19.

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2. Materials and methods

2.1. Study design

A prospective observational design was used to assess the relationship between apoptosis and proliferation rates in individuals recently infected with SARS-CoV-2. The investigation extends to both pre and post vaccinations phases, allowing for comprehensive understanding of the dynamics between viral infection and cellular responses.

2.2. Participants selection

Peripheral blood cells were obtained from newly diagnosed COVID-19 patients admitted to the emergency rooms (ER) of different private clinics in the Central Region of the Kingdom of Saudi Arabia (KSA). Healthy control samples were run in parallel. Coronavirus infection was confirmed by PCR run by the Ministry of Health.

Blood samples were obtained from 20 Coronavirus patients. Patients were between 15 and 45 years of age. All patients signed a consent form agreeing to donate blood for research purposes. All the 20 patients were KSA citizens. The group comprised thirteen males and seven females who were all from Riyadh City, KSA)Table 1).

2.2.1. Inclusion criteria

- Newly diagnosed patients;
- Unvaccinated patients.

2.2.2. Exclusion criteria

- Cancer patients;
- Children below 15 years of age; and
- Immunocompromised patients.

2.3. Ethical approval and inform consent

All 20 patients were briefed about the purpose of the study. Inform consent were taken from the participants stating their willingness to donate blood sample for study purposes. The consent form outlined the nature of study, potential risks, and ensured confidentiality of participants' information.

2.4. Sample collection

Peripheral blood cells were collected from the patients infected with COVID-19 virus and healthy controls for comparative analysis. The confirmation of COVID-19 virus was established through PCR conducted by Ministry of Health. Blood samples were processes to isolate mononuclear and polymorphonnuclear leukocytes for subsequent experimental procedure.

2.5. Isolation of mononuclear and polymorphonuclear leukocytes from human peripheral blood

Peripheral blood was obtained from COVID-19 patients and healthy donors (HD). Using complete medium (RPMI + 10 % FCS), blood was diluted 1:1. The diluted blood was then layered onto the surface of an equal volume of Lymphoprep^{TM} (Nycomed Pharma), and the gradient was centrifuged at 447g room temperature for 20 min. Peripheral blood mononuclear cells (PBMCs) were obtained from the interface cell layer and washed three times in a complete medium by centrifugation at 252g at 4 °C for 5 min. PBMCs were counted using trypan blue (0.4 %; Sigma) to enumerate viable cells using a hemocytometer. A certified phlebotomist collected blood on the same day as the isolation from patients and/or healthy volunteers with IRB approval. The sample collection process takes ten minutes (Cui et al., 2021).

Table 1
Participant Details.

Category	Sex	Frequency	Mean Age
Covid-19 patients	Males	13	29 years
	Females	7	
Healthy Controls	Males	20	33 years

2.6. Bronchoscopy procedure

The bronchoscopy procedure was conducted for one COVID-19 patient identified through real time reverse transcriptase PCR (RT-PCR). Ethical considerations and approval were diligently observed throughout this process. The bronchoscopy aimed to provide a deeper understanding of viral dynamics within respiratory system, contributing to crucial insight in to study. Bronchoscopy is a safe procedure with an extremely low mortality risk (between 0 % and 0.1 %), according to several studies (Dweik,et al., 1996) It was recently discovered that, as long as the patient doesn't have active ischemia during the surgery, bronchoscopy can be safely done after a recent myocardial infarction (Alamoudi et al., 2000).

2.7. Proliferation assay

Throughout 2020–2021, a proliferation assay for measuring COVID-19 replication was improved. The virus was very infectious, and the preferred course of action was not to use cell cultures and/or animal reservoirs to quantify its true effects on humans. Given the limited technical and facility resources, a novel assay to quantify its replication was developed. This technique was a procedure involving the combination of an enzyme-linked ImmunoSpot (ELISpot) assay and a mathematical formula employed on a Macintosh computer. This two-step technique was employed to further our understanding of viral dynamics during its first two weeks. The AUC was calculated to measure alveolar macrophage with virus proliferative capacity.

2.8. Quantification of apoptotic leukocytes

2.8.1. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL technique)

PBMCs and nose rinse were each suspended in MM buffer and mixed for 10 min with an equal volume of 8 % paraformaldehyde. Cells were pelleted at 1800 rpm for 5 min and then resuspended in Dulbecco's MEM (Gibco) at a concentration of 2 x 10^5/ml. Aliquots of 100 ml were cytocentrifuged (ShandonCytospin 2, Shandon, Pittsburgh, PA, USA) onto cleaned microscope slides at 450 rpm for 10 min. Quantification of apoptotic cells was measured by the TUNEL technique (Frag EL, Calbiochem, Nottingham, UK) as per the manufacturer's instructions. Numerous businesses offer "apoptosis detection" kits that use the TdT enzyme to identify DNA breaks. Nevertheless, using these tools to detect DNA breaks does not guarantee that apoptosis has occurred (Sies and Haeussinger, 2007).

2.9. Determination of soluble FasL (sFasL) in plasma by ELISA

Soluble FasL in serum samples was detected with a Sandwich ELISA kit (R&D Systems, MN, USA), set up according to the manufacturer's instructions without modification.

2.10. Luminex for IL-38

Plasma from both groups of patients was collected and stored at −20 °C for later analysis. Luminex kits used to analyze patients' plasma were purchased (Merck Millipore's MILLIPLEX MAP Human) and utilized as per the manufacturer's instructions.

2.11. Survinin by immunohistochemistry and ELISA

Cytospin sections were cut from frozen lung tissues from COVID-19 patients and placed on silane-coated slides. Survivin was detected by immunocytochemical technique (ABC procedure) and ELISA as per manufacturer's instructions (AF886, R&D Systems, Germany).

2.12. Vaccination

All subjects did not receive the vaccine. However, all ten healthy donors had previously received two doses each of COVID-19 vaccine (Pfizer-BioNTech). Laboratory investigations were carried out on them one month after their 2nd dose of vaccination.

2.13. Statistical analysis

The statistical techniques involved the use of Microsoft Excel and StatView SE + Graphics software. Graphs were plotted using a graphics package (CricketGraph).To ensure the robust and meaningful interpretation of the results, the study employed the appropriate statistical test including. The significance level chosen for the study was set at 0.05, adhering to the standard threshold for statistical significance. This rigorous statistical approach aimed to provide a reliable foundation for drawing conclusion and implication from the observed variation in apoptosis and proliferation rates among the study groups. Every statistical test's underlying assumptions were thoroughly examined to guarantee the accuracy of the findings. Graphs or suitable statistical tests were used to evaluate the homogeneity of variances and the normality of data distributions. Robustness tests were run or alternative statistical techniques were taken into consideration in situations when the assumptions were not fully met.

3. Results

3.1. Characteristics of participants

Table 1 shows details of participants categorized into COVID-19 patients and healthy controls, with further details based on gender. The data indicates that there are 13 men and 7 women among Covid-19 patients. The average age of male COVID-19 patients was 29 years. However, the average age of COVID-19 patients is not explicitly mentioned in the table. For healthy controls, there were 20 male participants with a mean age of 33 years.

3.2. Study of apoptosis in WBC from COVID-19 patients

A significant increase was found in the level of apoptosis in fresh, intact lymphocytes and granulocytes derived from COVID-19 patients compared to healthy donors (Table 2).

3.3. Corona increased the proliferation and apoptosis of human bronchial epithelial cells (also called large airways)

COVID-19 substantially increases the rate of proliferation and apoptosis of human bronchial epithelial cells. The level of proliferation from different samples was measured using the AUC. A significant level of proliferation of lung epithelial cells (LE) compared to healthy controls was found. Additionally, a significant level of apoptosis in COVID-19 patients was found compared to the healthy controls (Table 2).

3.4. Level of soluble FasL in plasma from COVID-19 patients

Compared to healthy donors, a slight increase in sFasL level in COVID-19 patients (1.62 ± 0.29 ng/ml *vs*. 1.38 + 0.06 ng/ml respectively). The level of sFasL decreased in COVID-19 patients treated with dexamethasone (1.1 ± 0.4 ng/ml) compared to those treated with anti-inflammatory drugs only (1.9 ± 0.2 ng/ml). A significant elevation of pro-inflammatory cytokine (IL-38) levels in COVID-19 positive patients, compared to the normal healthy control group, was found (Table 3).

3.5. Survinin by IHC and ELISA

Survivin was measured using ELISA and was significantly higher in those who took the vaccine and/or recovered from COVID-19 infection than those at week one of infection. Survivin was also detected and confirmed by immunohistochemistry in one sample obtained from a lung biopsy (bronchoscopy procedure; Table 4).

4. Discussion

4.1. Apoptosis in WBC cells and survivin

This study has shown that WBC cells from COVID-19 patients are more prone to die by apoptosis. It was found that blocking caspase activation using survivin prevented WBC cells from dying and supported pro-inflammatory cytokine production. Like the strategy used by many other viruses, COVID-19 promotes apoptosis to survive and maintains its reservoir via a Fas-mediated mechanism (Paolini et al., 2021; Zhou et al., 2017; Poole et al., 2015; Seirafian et al., 2014).

4.2. Immuninological dynamics in COVID-19

This airway inflammation caused by COVID-19 is a balance mechanism between IL and 38 production by airway epithelial cells and IL-10 by apoptotic cells (unpublished data from Prof. M.W. Alrabea, King Abdulaziz University, KSA).

It was previously found that T-cell apoptosis was associated with a lower B-cell response (Seirafian et al., 2014), interestingly similar to during an Ebola virus infection. In the current study, it was reported how survivin prevents WBC cell apoptosis, a process likely to help reduce the severity of the disease and improve outcomes. This conjecture is supported by a recent publication demonstrating that the blocking of Th1 cytokines reduces the pathogenesis of COVID-19 in mice (Karki et al., 2021; André et al., 2022).

Since all patients were neither ER patients nor under corticosteroid therapy and/or cytotoxic drugs, it was clear that apoptosis of WBC represents a vital role in viral pathogenesis. One may assume that the level of DNA damage in leukocytes indicates the severity of the disease. The increased level of apoptotic lymphocytes was consistent with leukopenia. Additionally, increased expression of sFasL induces apoptosis in Fas-expressing cells, which supports the *in vitro*

Table 3
Levels of IL-38 Pro-inflammatory Cytokine.

Group investigated	IL-38(Mean ± SD)
Normal controls (n = 20)	1.5 ± 2
Covid-19 Patients (n = 20)	2.8 ± 0.9

Table 2
Levels of Apoptosis and Proliferation(human bronchial epithelial cells).

Category	Apoptosis Sample size	% Apoptosis100% −(M + SD)	Proliferation Sample size	% Proliferation 100 % −(M + SD)
Covid-19 Patients	20	14 ± 3.2	20	82 ± 7.2
Normal controls	20	1.8 ± 9.1	20	21.2 ± 1.7

Table 4
Levels of Survivin.

Group investigated	Survivin(Mean ± SD)
Vaccinated/Recovered **(n = 20)**	9.0 ± 2.0
Covid-19 Patients (n = 20)	3.5 ± 0.8

experimental demonstration of increased apoptosis in lymphocytes (Garrone et al., 1995). Therefore, this stimulated interest in studying the role of sFasL in regulating apoptosis in WBCs (Bijl et al., 1998; Miret et al., 2001; Silvestris et al., 2003).

4.3. sFasL-mediated pathways in COVID-19 immunopathology

The current study found higher plasma sFasL, where later FasL is upregulated in activated T cells, leading to WBC depletion (Bonfoco et al., 1998; Kuwano et al., 1999; Hamann et al., 1998). It is known that sFasL may be released as a biologically active death-inducing mediator capable of inducing apoptosis during an episode of acute lung injury (Matute et al., 1999); metallopeptidases (including MMP7 and also ADAM10) are responsible for FasL cleavage. The study did not involve measurement of any relationship between plasma sFasL and the number of depleted T cells. However, this might be consistent with the idea that survivin could offer a beneficial therapeutic effect by reducing the lung damage typically observed in COVID-19 infections (André et al., 2022).

In earlier research, a significant role for the Fas-FasL pathway in regulating myelopoiesis and in the context of CML, was reported. Currently, neither during inflammation nor in the context of homeostasis is the signaling modality of FasL to Fas particularly well understood. sFasL acts as a pro-survival signal, but mFasL induces apoptosis. In the current study, however, it was determined that sFasL does kill WBC cells (Schweizer et al., 2021; Alenzi et al., 2005; Alenzi et al., 2002).

In other contexts, sFasL acts as a pro-survival signal for neutrophils as part of the overall process of TNF-α mediated necroptosis, but its expression and secretion are altered during a COVID-19 infection (Schweizer et al., 2021).

It was believed that the Fas-FasL interaction expressed in COVID-19 peripheral blood T patients kills Fas-expressing cells. Here, it was demonstrated that sFas ligand (sFasL) kills fresh PBT, indicating that the Fas expressed on freshly infected cells PBL is functional (T Suda et al., 1997).

Leukopenia was also noticed in these patients and correlated with disease severity.

The results showed increased levels of plasma sFasL on the WBC of COVID-19 infected individuals. This finding is consistent with previous reports (André et al., 2022).

In parallel with these findings, the presence of lymphopenia was demonstrated. It was felt as relevant to check whether a negative or positive correlation occurred between T cell counts and sFasL concentrations; however, this was not observed.

4.4. Role of cytokine storm and IL-38 in COVID-19 pathogenesis

Several cell types, including Th, DC, macrophages, and others (i.e., a "cytokine storm"), can produce cytokines. This phenomenon involves many molecules, growth factors, apoptosis factors, and pro- and anti-inflammatory proteins (Paolini et al., 2021; Y-M Gao et al., 2021; Gibellini et al., 2020; Sica et al., 2019; Silvin et al., 2020). Up to now, 20 years since its discovery, many issues about this phenomenon remain unclear. Interleukin-38 (IL-38) represents the most recently described member of the IL-1 family. It reduces and resolves many chronic inflammatory diseases (Wang et al., 2018). On the contrary, cell death may lead to inflammation by generating pro-inflammatory molecules. Mora et al. determined levels of IL-38 from apoptotic lung and breast cancer cells (Gregory et al., 2011; Fazeli et al., 2022) and found results similar to those reported here.

Additionally, it was thought that IL-38 regulates the JAK-STAT pathway, thereby potentiating inflammatory processes (SonuBhaskar et al., 2020; Panigrahy et al., 2020; Favalli et al., 2020). On the contrary, other researchers believe IL-38 inhibits MAPK signaling, inhibiting cytokine activation through this biochemical route (Mohsin et al., 2021; Pavord et al., 2017; Queen et al., 2019; Boutet et al., 2019; Madonna et al., 2019; Bassoy et al., 2018).

It is thought that the infection of lymphocytes in COVID-19 patients leads to a cytokine storm. Therefore, targeting a cytokine storm may improve the outcome of COVID-19 patients (SonuBhaskar et al., 2020, Wong et al., 2003; Leng et al., 2020). IL-38 activation and WBC apoptosis may be linked with leukopenia in patients with COVID-19 infections (André et al., 2022).

4.5. Correlation between sFasL and IL-38

The observed correlation of sFasL with increased IL-38 (the twin of IL-1) could be interpreted to imply that neutrophil WBC apoptosis (in the context of decreased sFasL levels) might favor an inflammation feedback loop which creates a central role for IL-6 signaling; if so, this might potentially sustain an emergency granulopoiesis capable of aborting lymphopoiesis (Schweizer et al., 2021; Garraud et al., 2018; Fielding et al., 2008; Maeda et al., 2009).

4.6. Epidemiological trends of COVID-19 in KSA

The current study represents the first report of the effect of survivin in patients with coronavirus patients. Many issues related to survivin, and its binding to caspases, are not yet understood. However, at least two papers have shown that survivin is an efficient caspase inhibitor and suppresses apoptosis (Srinivasula et al., 2008; Marianna et al., 2021; Yuan et al., 2015). During viral infections, apoptosis is activated by caspase-3 and caspase-9, which can be through either the intrinsic (mitochondrial) or the extrinsic (Fas) pathway. On the other hand, survivin is important for mitochondrial function and integrity (Liu et al., 2015), as it inhibits terminal caspases (Pavlyukov et al., 2011). Accordingly, it is fair to say that the activation of both caspases and survivin is not yet fully understood. When phosphorylated, survivin acts as an anti-apoptotic protein, binding to caspase-9 (Marusawa et al., 2003). In our system, survivin is upregulated in those who took the vaccine to maintain the host's survival, which is one possible explanation, thereby supporting the host from "danger signals" activating both arms of the immune system (Srinivasula et al., 2008, Tavladaki et al., 2017; Fitrolaki et al., 2016).

With variable degrees of severity in different countries, COVID-19 has become one of the most important worldwide health challenges in recent years, raising major health and economical implications. One of the nations afflicted by the virus was Saudi Arabia (KSA), where the Saudi Ministry of Health announced the first case of COVID-19 in March 2020. As the nation's verified case count progressively rose, people, families, and the federal government all began to fear. The government implemented stringent evaluation and control measures, including the cancellation of religious, recreational, sporting, and commercial gatherings, in an effort to stop the virus's spread. Following that, there was a decrease in infection rates, an increase in recovery rates, and a decrease in fatality rates.

June and July 2020 saw a dramatic spike in mortality, according to another recent report. Because Riyadh and other major cities have many commercial hubs and entertainment venues, we have also seen a higher prevalence of cases in these high population density areas. On the other hand, COVID-19 instances were less common in smaller, less populous places (data not shown). Later, in an effort to slow its growth, extensive evaluation and control procedures were put in place, such as the cancellation of religious, recreational, sporting activities, and commercial meetings. On March 5, 2020, the Kingdom of Saudi Arabia (KSA)

announced more limitations, stating that the Prophet's Mosque and the Grand Mosque in Makkah would be closed to reduce crowding and sterilise. The incidence and fatality cases were increasing in spite of all the restrictions. 2020 June and July saw the highest number of deaths, according on our data. In order to stop the illness from spreading, KSA thereupon announced a work stoppage in all public and private sectors, with the exception of security, catering, pharmacies, food shops, petrol stations, and the medical field. Almost all control measures had been lifted by September 2021, and COVID-19 had dropped to an obviously low level.

The majority of COVID-19 cases were reported in industrialized, sizable cities like Riyadh. Its massive population, countless complexes, commercial centers, and entertainment venues could be the cause of such. In contrast, because of their tiny populations, we discovered fewer cases in limited locations. Increased IL-1b, which is linked to ARDS, was present in the majority of COVID-19 patients with serious sickness. Likewise, early IL-1 receptor blocking was discovered to be a viable treatment approach against the cytokine storm-induced inflammation that causes respiratory distress in COVID-19 patients.

An effective therapeutic option was demonstrated for COVID-19 patients who were at risk of developing cytokine storms by targeting IL-6 receptors (IL-6r) with a specific monoclonal antibody, tocilizumab. It was reported that elevated levels of IL-6 exacerbate the inflammatory process while contributing to the cytokine storm, thereby worsening prognosis (14). Different patterns in COVID-19-related disease incidence, rehabilitation, and death rate have recently been shown. Since that the same preventive protocols and restriction measures were implemented throughout the Kingdom of Saudi Arabia, variations in people' adherence to these measures may be the cause of this trend variation.

Furthermore, there were significant differences between the number of people densities of various cities. Across Saudi Arabian counties, there is also a significant variation in the national variety of the population. The individuals' disparate cultural origins are another important element. Due to hereditary and other factors, this may result in varying degrees of protocol adherence as well as distinct endemic epidemiological distributions. Different views, understandings, and practices around the disease would result from this diversity. In some small cities, access to reporting systems may be limited, and despite efforts to educate the public, there may still be a knowledge gap.

The epidemiological status of COVID-19 in KSA, including infection, mortality, and recovery rates, was described in this study. COVID-19 displayed a variable rate of active illness over time, which was indicative of a well-functioning medical system and treatment plan. Restrictions on travel abroad and home quarantines also contributed to the disease's delayed spread. As the number of instances rose, new protocols were developed and put into effect right away. Preschools, schools, and universities all shifted their course offerings to online formats. The majority of organizations used postal delivery and online buying. Every administration's or province's authorities were free to take further actions that were necessary given the situation.

To curb the spread of COVID-19, for instance, the Saudi Arabian government ceased providing visas for Umrah to any international visitors. This was followed by a suspension of Umrah for everyone. The available data indicates that between May 2020 and November 2021, there was a significant decline in the number of verified cases and fatalities, but the recovery rate remained continuously high.

Although the recovery stage was briefly interrupted between May and July 2021, in line with the SARS-CoV-2 s wave reports, the government's quick responses and stringent measures—such as the nationwide lockdown, travel restrictions, and social distancing guidelines—were successful in preventing the virus's ability to spread. As a result, the number of confirmed cases as well as fatalities declined in the months that followed. Additionally, the study used Spearman's rank correlation coefficient to look at the rates of new infections and fatalities in the US, UK, and Saudi Arabia.

Vaccination was the main factor in keeping COVID-19 contained in Saudi Arabia. As soon as the vaccine was released, it was made available to all citizens of the nation without payment. The immunization program was well-organized and accessible to all inhabitants and citizens. The successful COVID-19 vaccination and treatment regimens, in addition to precautionary and control measures, were efficient means of controlling the COVID-19 pandemic in the Kingdom of Saudi Arabia.

Furthermore, vaccination is a significant strategy for stopping the COVID-19 virus from spreading and lessening its effects on public health. KSA places a significant priority on public health, as seen by the high rates of adult and pediatric COVID-19 vaccinations. Public health standards must be strictly adhered to by the general public, and immunization initiatives must continue. It is reasonable to assume that if the public, medical professionals, and government continue to collaborate, KSA will be able to effectively manage the challenges presented by COVID-19 and enhance its capacity to react to future health emergencies.

5. Limitations

While the findings in the current study came from a relatively small cohort at two institution, they do further help elucidate what appears to be a crucial role of the Fas/FasL system during a COVID-19 infection. They may also suggest and provide tools for future therapeutic development (26).

6. Conclusion

In conclusion, our research shows that SARS-CoV-2 infection and apoptotic WBC cell death in COVID-19 patients are related. It has been demonstrated that survivin can impede this process, pointing to a possible treatment approach to stop lymphopenia and lessen the severity of the illness. The results highlight the need for more investigation to clarify the function of apoptosis in COVID-19 pathogenicity and investigate focused therapies. In the future, developing an understanding of the mechanisms behind WBC apoptosis may help develop new therapeutic strategies and improve COVID-19 patient care.

CRediT authorship contribution statement

Faris Qb Alenzi: Writing – original draft, Project administration, Investigation, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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