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Helping doctors hasten COVID-19 treatment: Towards a rescue framework for the transfusion of best convalescent plasma to the most critical patients based on biological requirements via ml and novel MCDM methods

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ABSTRACT

Context: People who have recently recovered from the threat of deteriorating coronavirus disease-2019 (COVID-19) have antibodies to the coronavirus circulating in their blood. Thus, the transfusion of these antibodies to deteriorating patients could theoretically help boost their immune system. Biologically, two challenges need to be surmounted to allow convalescent plasma (CP) transfusion to rescue the most severe COVID-19 patients. First, convalescent subjects must meet donor selection plasma criteria and comply with national health requirements and known standard routine procedures. Second, multi-criteria decision-making (MCDM) problems should be considered in the selection of the most suitable CP and the prioritisation of patients with COVID-19.

Objective: This paper presents a rescue framework for the transfusion of the best CP to the most critical patients with COVID-19 on the basis of biological requirements by using machine learning and novel MCDM methods.

Method: The proposed framework is illustrated on the basis of two distinct and consecutive phases (i.e. testing and development). In testing, ABO compatibility is assessed after classifying donors into the four blood types, namely, A, B, AB and O, to indicate the suitability and safety of plasma for administration in order to refine the CP tested list repository. The development phase includes patient and donor sides. In the patient side, prioritisation is performed using a contracted patient decision matrix constructed between 'serological/protein biomarkers and the ratio of the partial pressure of oxygen in arterial blood to fractional inspired oxygen criteria' and 'patient list based on novel MCDM method known as subjective and objective decision by opinion score method'. Then, the patients with the most urgent need are classified into the four blood types and matched with a tested CP list from the test phase in the donor side. Thereafter, the prioritisation of CP tested list is performed using the contracted CP decision matrix.

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Result: An intelligence-integrated concept is proposed to identify the most appropriate CP for corresponding prioritised patients with COVID-19 to help doctors hasten treatments.

Discussion: The proposed framework implies the benefits of providing effective care and prevention of the extremely rapidly spreading COVID-19 from affecting patients and the medical sector.

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1. Challenges of biological requirements

Antibody immunisation has been performed since the 20th century to prevent and/or treat infectious diseases; throughout the years, its lifesaving ability has been proven in many critical cases [1]. Convalescent blood products (CBPs) are obtained by collecting plasma from a patient who has recovered from a viral or bacterial infection and has developed immunity against the pathogen that caused the disease [2]. When transfused, CBPs can neutralise viruses and bacteria, thus suppressing them in the blood [3]. This method was used to treat influenza A (H1N1) virus and was effective in reducing H1N1 load and decreasing the mortality rate [4]. Ebola virus is a recent example of the successful application of CBP for patients in areas with high mortality rate [5,6].

Similarly, the use of antibodies from patients who recovered from coronavirus disease-2019 (COVID-19) can be the main approach for the prevention and treatment of the extremely rapidly spreading virus [7]. For plasma protein therapies, general safety measures have been established regarding plasma collection from donors. SARS-CoV-2 is a large virus (approximately 120 nm in diameter). Its relatively large size and lipid envelope make it highly susceptible to viral inactivation and removal capacity steps during manufacturing processes, such as solvent-detergent processing [8], low-pH incubation, caprylate incubation, pasteurisation [9], dry-heat treatment [10], nanofiltration and fractionation [11]. Plasma or immunoglobulins collected from patients who recovered from a viral infection, such as COVID-19, have been used as a last resort to improve the survival rate of patients with the novel coronavirus whose conditions have continued to deteriorate despite treatment with pulsed methylprednisolone [12]. Patients treated with convalescent plasma (CP) demonstrate shorter hospital stay and lower mortality compared with those not treated with CP; work is ongoing to test this theory on patients with COVID-19 [12,13]. People who have recently recovered from COVID-19 have antibodies to the coronavirus circulating in their blood. Transferring those antibodies into deteriorating patients could theoretically help boost their immunity [14,15]. CP administration to patients with COVID-19 improves their clinical conditions and decreases lung lesions [16]. Given scarce information on the biology and mode of infection of COVID-19 and the virus' ability to reproduce itself via mutation, plasma collected from recovered patients that meet clinical criteria may offer a valuable treatment option [17]. However, the low number of recovered COVID-19 cases and their ability and eligibility for plasma donation make the implementation of this strategy difficult.

The CP of eligible donors in areas where an epidemic disease has broken out can offer specific, artificially obtained, passive immunity against the local infectious agent [18]. Plasma protein levels can readily be affected by bacterial and viral infections [19]. Identifying specific viral protein biomarkers is a possible strategy to identify sources and types of infection [20]. Regular donor screening procedures should be performed to prevent individuals that show disease symptoms generally associated with coronavirus infection, including COVID-19, from donating their plasma. In general, age, gender and weight must be considered for plasma donor selection [21]. Specifically, pooled plasma from recovered COVID-

19 donors for anti-COVID-19 antibody therapy may undergo several general tests that can be divided into two challenging stages.

The first stage involves general plasma requirements. Plasma first undergoes polymerase chain reaction (PCR) testing to detect viral genomes (COVID-19, HIV, HBV and HCV), which should be negative [22,23]. Depending on the result, the plasma sample could undergo viral inactivation treatments, such as solvent-detergent incubation, which is the most commonly used method [24,25]. The second stage is the evaluation of plasma suitability/efficacy by using protein biomarkers that indicate the safety/suitability of plasma. These biomarkers include serum protein and albumin concentrations of 60 and 35–50 g/l, respectively. Furthermore, IgM and IgG levels should be at least 0.5 g/l and within 5–20 g/l, respectively [22,23,26]. Other infection-related proteins in plasma, such as peroxiredoxin II [27,28] and cytokines and chemokines (IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNF α), should be at normal levels [29,30]. The level of plasma C-reactive protein has been used as a marker to differentiate between severe and non-severe cases of COVID-19 [31,32]. The ratio of the partial pressure of oxygen in arterial blood to fractional inspired oxygen (PaO₂/FiO₂) is used to determine the level of respiratory distress (200–300 for mild, 100–200 for moderate and below 100 as severe) in patients with COVID-19 [33,34].

Finding and selecting eligible donors with a sufficient amount of plasma for efficient utilisation can be challenging as convalescent subjects must meet the donor selection and general plasma requirements in the first stage. Furthermore, the selection of the best CP to the most critical patients with COVID-19 is challenging because the requirements in the second stage should be followed whilst considering blood types; this process is considered a problem of multi-criteria decision-making (MCDM), which complies with national health requirements and known standard routine procedures [35]. Moreover, intelligent computing issues should be investigated to propose a fully automated intelligent computing framework to solve these complex challenges.

2. Intelligent computing issues

A fully automated intelligent computing solution framework for the abovementioned challenges can be established by following critical reviews related to intelligent computing issues on the basis of two directions, namely, classification of blood types and prioritisation in the medical sector.

Firstly, blood type classification is crucial for medical procedures such as blood transfusions. Before conducting medical procedures, a wide range of compatibility tests called pre-transfusion tests must be conducted [36]. However, time is often limited in case of emergencies, preventing these experiments to be performed using commercial systems available in laboratories; this scenario might result in transfusion reactions, which may worsen the condition of patients or lead to death [37]. Other manual alternatives allow blood type determination; however, these procedures require a laboratory technician to intervene and are susceptible to human error during either testing or reading and interpreting findings, which are not acceptable in crucial cases [38]. In these cases, pre-transfusion tests are often appropriate even in emergency situations, and compatible blood should be administered to eradicate

blood incompatibilities. Furthermore, the universal blood type for donors is not too infrequent. Research efforts on classifying blood types in these cases are scarce.

The author of [38] developed a prototype for the rapid determination of blood pre-transfusion tests in emergency situations. This prototype is portable, effective and affordable can be used even in remote locations and undeveloped countries; it has been used in remote areas, ambulances, far-off accident sites and areas struck by natural disasters (e.g. tornados, earthquakes, tsunamis and wars). Another author [39] discussed the importance of classifying blood type by presenting an image processing-based methodology that allows the rapid (i.e. 2 min) and safe determination of a patient's blood type for use in emergency cases. They effectively utilised their methodology and verified its capability to safely and rapidly identify blood types for use in emergencies [40]. The blood types can be determined using their techniques by plate tests, and the analysis can be carried out automatically. Furthermore, they discussed that image processing methods can enable automatic identification with fast and accurate blood type results; the use of such approach would eliminate errors committed by technicians in blood typing, leading to safe blood transfusions and reducing the loss of human lives [41].

Authors [42] introduced a prototype for pre-transfusion testing that was designed exclusively for use in emergencies. The prototype is unique in its portability, effectiveness and timely results. The latest version of the prototype introduced significant improvements concerning various factors, such as size, optimised plate test, high autonomy, light weight and reduced execution time for procedures. These research efforts clearly indicate that blood type determination is not a new topic and should be performed rapidly and efficiently without producing errors in dangerous situations. Given the recent spread of COVID-19, hospitals are filled with numerous patients who are either improving from the viral infection or getting worse (dying). However, plasma from those who recovered can be used to assist those who have not recovered depending on their severity. In this case, blood type classification should be performed with maximum speed and efficiency to save as many lives as possible. The role of intelligent technologies, such as machine learning (ML) methods (e.g. naive Bayes, nearest neighbour, support vector machines and decision trees) and deep learning methods (e.g. deep, artificial, convolutional and recurrent neural networks), would help the classification process, the management of such patients and in deciding donor plasma prioritisation.

Secondly, patient prioritisation in the medical sector is conducted to provide health care/services for each patient in due course. On the basis of the severity of patient condition, rescuers determine and provide suitable healthcare services depending on patient priority [43]. In an emergency, the highest and lowest priorities should be given to patients with the most and least emergent case, respectively, compared with other patients in the healthcare system. Improper patient prioritisation can lead to incorrect strategic decisions that can endanger patients' lives [44]. Several medical informatics studies have presented a prioritisation solution for patients with single [46–48] and multiple chronic heart diseases [49–51].

Furthermore, the healthcare sector is affected by numerous patients with COVID-19 and needs an urgent solution to avert the risk of deteriorating patients in terms of their prioritisation according to their critical health conditions. A study [52] proposed a methodology to select situations with risky health conditions and prioritise patients depending on laboratory examination results. This process is highly complex, especially when a decision rule based on multi-biological requirements is followed, thereby introducing another challenge [53]. The exact situation for all infected patients should be understood on the basis of all criteria. In this case, patients infected with COVID-19 should be prioritised

in order to administer appropriate treatments from critical to mild situations [54]. This process enables infectious disease specialists to differentiate patient levels and detect optimal asymptomatic carriers amongst other critical patients [55,56].

No study has presented a distinct and successive prioritisation solution for patients with COVID-19 and CP recipients nor provided an appropriate health care/treatment based on their priority situation. Three specific issues of the prioritisation of patients with COVID-19 and CPs are described as follows. Firstly, the prioritisation is dependant on important attributes; thus, patient and CP selection based on multiple criteria is a multi-attribute decision matrix [57–61]. Secondly, different values of importance are often given for each attribute, which further increases the complexity of the task [63–67]. Finally, a prioritisation process requires synchronised consideration of the inverse relationship amongst the mentioned criteria; thus, a trade-off is created [49,68], [122]. In this context, decision-making methods are essential to overcome the abovementioned challenges by prioritising infected patients with COVID-19 and CPs.

MCDM is an extension of decision theory covering any multi-objective decision and can solve this problem by constructing a decision matrix based on an intersection between the evaluation criteria used and patients with COVID-19 and/or a list of tested CPs. In general, the main target of MCDM is to rank/prioritise a set of alternatives on the basis of different evaluation criteria [63,69–74].

To the best of our knowledge, no study has covered the challenges and issues in terms of biological requirements and intelligent computing on automation framework. Thus, a transfusion framework should be proposed to help doctors hasten treatments. The framework should include general plasma requirements, a minimum of two viral reduction steps and the use of protein biomarkers to indicate the safety and suitability of plasma. Furthermore, the framework should include a process for selecting patients with the most critical emergency condition and the best CP on the basis of biomarker criteria whilst utilising MCDM methods. These methods should be used to weigh the evaluation criteria and prioritise COVID-19 plasma on the basis of blood types. In such case, transfusion can be achieved from donor to patient on the basis of patients' critical health conditions and priority.

3. Conceptual framework

The proposed framework is illustrated on the basis of two distinct and consecutive phases (i.e. testing and development). In testing, ABO compatibility is achieved after classifying donors into the four blood types, namely, A, B, AB and O, to indicate the suitability and safety of plasma for administration and refine the list of tested CPs (Fig. 1). The development phase includes patient and donor sides. On the patient side, prioritisation is performed using a contracted patient decision matrix between the serological/protein biomarkers and $\text{PaO}_2/\text{FiO}_2$ and patient list via a novel MCDM method called subjective and objective decision by opinion score method (SODOSM). Then, the patients requiring the highest emergency are classified on the basis of their blood type to be matched with the list of tested CPs from the test phase on the donor side. Then, the list of tested CPs is prioritised using the contracted CP decision matrix (Fig. 2).

3.1. Testing phase

Plasma protein levels can readily be affected by bacterial and viral infections [19]. However, specific viral protein biomarkers can be used to identify the source and type of infections [20]. Standard donor screening procedures should be followed to avoid plasma

Fig. 1. Pooled plasma from recovered COVID-19 donors for use in anti-COVID-19 antibody therapy should undergo a two-stage test.

Fig. 2. Intelligence-integrated concept to identify the most appropriate CP for a corresponding prioritised patient with COVID-19.

donations from people that display clinical symptoms typically linked to coronavirus infection, including COVID-19. In general, pooled plasma from recovered COVID-19 donors for anti-COVID-19 antibody therapy should undergo a two-stage ABO compatibility test (Fig. 1). Pre-transfusion testing is essential before blood transfusion from donors to patients. The detection of agglutination in blood samples and the correct determination of blood type through ML methods are effective. Patient classification at this phase can be performed using several approaches based on image acquisition, processing and ML methods. Through these different classifiers, accurate blood type results can be achieved. This classifier will manage donors at the start of the process (Fig. 1) and classify them on the basis of their blood types. The list of donors who had their plasma tested for blood typing and who were successful in the test stages and collected in repository #1 should be determined and show beneficial results on further steps (Fig. 2). Practical steps will be explained in detail in the development phase.

The first stage explains the general plasma requirements and the following viral reduction steps. (1) PCR is used to detect viral genomes (e.g. COVID-19, HIV, HBV, HCV), which should be negative; alternatively, other methods approved by local medical authorities can be used [22,23]. (2) Viral inactivation/fractionation treatments, such as solvent-detergent incubation, are used. (3) Viral heat deactivation or filtration is also used.

The second stage involves the use of the following protein biomarkers to indicate the safety and suitability of plasma: (1) total serum protein concentration of 60 g/l; (2) albumin concentration within 35–50 g/l; (3) minimum IgM and IgG level of 0.5 and within 5–20 g/l, respectively [22,23,26]; (4) normal plasma peroxiredoxin II level (relative to that of a non-infected individual) given that a high [28] or low [27] level may indicate that a plasma is unsuitable for donation/therapy; (5) normal plasma level of cytokines and chemokines (elevated levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNF α indicate severe lung inflammation) [29,30]; and (6) plasma C-reactive protein can differentiate severe from non-severe cases. The C-reactive protein is highly elevated in severe COVID-19 cases [31,32].

The outcome of stage 1 is that either a patient is registered in repository #2 due to positive HCV test or referred to stage 2 due to negative HCV test. Stage 2 begins by testing for anti-COVID-19 antibodies/biomarkers. The outcome of stage 2 involves two repositories. Repository #3 is considered for non-eligible donors. The most important repository is #1, wherein a donor has passed the tests related to this stage. This repository will involve a useful CP that can be used for further processing (Fig. 2).

3.2. Development phase

This phase manages the list of tested CPs resulting from the test phase and repositories of the infected patients. It involves two intelligent concepts. Section 3.2.1 explains the ML methods used for classifying blood types for infection repository. Section 3.2.2 discusses the prioritisation of patients with COVID-19 and CPs by using the MCDM approach.

3.2.1. ML methods for classifying blood types for infection repository registration

The classification processes involve testing and development phases [75–79]. In the testing phase, donors with patient repository in the development phase are classified (Fig. 2). This phase aims to classify the most emergent patient into one of the four blood types (A, B, AB and O). The list of tested CPs that can be targeted from repository #1 (Fig. 2) in further processes should be determined. The blood classification steps shown in Fig. 3 for both phases can be explained as follows:

3.2.1.1. Step 1: data collection. In this step, the test results of collected blood samples will be converted into images for use in the next stage, which is preprocessing [78,80,81]. A person's blood type is determined by applying antigens A, B and D to the person's blood samples. These antigens may or may not match with red blood cell antibodies to a particular blood group. The technician detects clumps of blood cells after antigens are applied to the blood samples. For example, if clumps in samples with antigens A and D are detected, then the blood group is defined as A+. If the clumps are only found in samples applied with antigen A, then the group is marked as A-. Likewise, if clumps are produced in blood samples applied with antigens B and D, then the group is known as B+. If no clumping occurs in blood samples added with any of the antigens, then the group is known as O- [42].

3.2.1.2. Step 2: dataset preprocessing. In this step, the collected sample images must be aligned to one image containing three centred blood tests to preprocess the dataset and prepare it for ML. The image is a 30 × 90-pixel rectangle. Afterwards, the label should be changed from categorical to numerical. The dataset will be loaded to Python. The data arrays are reshaped to provide a single-colour display, and the collected images should be converted from RGB to greyscale. Eight groups are defined as specific integer groups. One hot encoding is performed to convert the integers into eight binary vector elements with 1 for a class value index and 0 for all other classes. Accordingly, for ML to understand our dataset,

Fig. 3. Classification steps.

the pixel values of each image in the dataset should be prepared as unsigned integers in the range between black and white or 0 and 255. The pixel values of greyscale images are then normalised (e.g. rescale them to the range [0,1]). This step first involves the conversion of the data form to floats from unsigned integers and then the division of the pixel values by a maximum value of 255. Moreover, the dataset will be divided into three sets, namely, training set with 70% of the total size, validation set with 15% of the total size and test set with 15% of the total size. The training set will be used to train via ML. The validation set will be used to validate the training in every epoch. Lastly, the test set will be used to evaluate the model after being trained. The next step will involve using these sets to train via ML.

3.2.1.3. Step 3: learning. This step includes building learning methods as previously explained. The dataset is loaded into Python and then separated into training, testing and validation sets, which will be used for learning training, validation of the model and evaluation of learning, respectively [82]. After training and testing, the learning will be used to classify new blood test samples. A good result will then be obtained by the ML classifier in image processing. Thus, each of the tests will establish whether or not sample agglutination has occurred.

3.2.1.4. Step 4: classification. This step uses the trained saved model in step three and then preprocesses the new image samples as in phase two, except for labelling, which will be predicted using our trained ML method. To classify the new blood test results on new images, the trained learning method will be used as a classifier method, which assumes that new images are greyscale and arranged in a manner wherein one picture contains three orientated blood tests (antigens A, B and D). The picture is a 30×90 -pixel rectangle.

3.2.2. Prioritisation of patients with COVID-19 and CPs via the MCDM approach

This section presents the prioritisation of patients with COVID-19 via MCDM methods. Section 3.2.2.1 proposes decision matrices of CPs and patients with COVID-19. Section 3.2.2.2 explains the development of a potential MCDM solution. Section 3.2.2.3 describes the methodology of the proposed novel MCDM method.

3.2.2.1. Proposal of prioritisation decision matrices of CPs and patients with COVID-19. A set of alternatives (i.e. patients with COVID-19) can be prioritised to transfuse CP to the most severe patients who cannot safely wait. At this stage, the patients will be prioritised on the basis of six serological/protein biomarkers and $\text{PaO}_2/\text{FiO}_2$ criteria (i.e. albumin, IgM/IgG, cytokine/chemokines, peroxiredoxin II, C-reactive protein, $\text{PaO}_2/\text{FiO}_2$). In this case, the patient decision

matrix is constructed on the basis of an intersection between serological/protein biomarker and $\text{PaO}_2/\text{FiO}_2$ criteria and patients with COVID-19 (Table 1).

As shown in Fig. 2 (patient side), the proposed patient decision matrix can be used to prioritise all patients with COVID-19 and identify the most critical patients that immediately require a compatible CP from donors. Before proceeding with a detailed explanation of CP transfusion to prioritised COVID-19 patients, we should explain the process of CP/blood donation. From a medical perspective [38], CP/blood donation can be performed as follows:

- 1 Volunteer class A can donate CP/blood to patient class A or B
- 2 Volunteer class B can donate CP/blood to patient class B or AB
- 3 Volunteer class AB can donate CP/blood only to patient class AB
- 4 Volunteer class O can donate CP/blood to all patients classes (i.e. A, B, AB, O)

On this basis, the most critical patient with COVID-19 has been prioritised, and the results from the mentioned patient decision matrix should also be classified for blood type identification. Moreover, as shown in Fig. 2 (donor side), the donors are classified into the four blood types. Now, we assume that we have obtained five CPs of class O, five patients with COVID-19 of class A and five patients of class B. The patient decision matrix is used and prioritises patients on the basis of their emergency conditions. For example, if patient 1 under class A is considered as the most critical and severe patient with COVID-19, then he/she immediately requires a suitable CP. An important question is: who is the most appropriate volunteer (five CPs under class O) that can donate CP for this critical patient (patient class A)? A CP decision matrix (Table 2) should be provided to prioritise and identify the most suitable volunteer that can provide an appropriate CP for the patient under class A.

In line with the patient decision matrix, the CP decision matrix is constructed on the basis of an intersection between the serological/protein biomarker criteria and the list of CPs tested. An overall evaluation criterion can be recognised under two categories, namely, benefit and cost. The benefit criterion implies that a high value is better, but the cost criterion implies the opposite [49,83–85]. In this study, from a medical perspective, albumin, IgM/IgG and $\text{PaO}_2/\text{FiO}_2$ levels are considered the benefit criteria, whereas cytokine/chemokine, peroxiredoxin II and C-reactive protein levels are considered the cost criteria. In summary, the mentioned decision matrices (i.e. patients and CP decision matrices) have been proposed to identify the most suitable CP within each class (donor side) for corresponding prioritised patients with COVID-19 (patient side). However, on the basis of the constructed decision matrices, three prioritisation issues have been generated (i.e. multi-criteria, important criteria and trade-off amongst the criteria). The prioritisation of patients with COVID-19 and/or CPs regarding multi-

Table 1

Decision matrix of patients with COVID-19.

Serological/protein biomarker and PaO ₂ /FiO ₂ criteria	C1	C2	C3	C4	C5	C6
COVID-19 patients						
Patient 1	C1M/P1	C2M/P1	C3M/P1	C4M/P1	C5M/P1	C6M/P1
Patient 2	C1M/P2	C2M/P2	C3M/P2	C4M/P2	C5M/P2	C6M/P2
⋮	⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮	⋮
Patient n	C1M/Pn	C2M/Pn	C3M/Pn	C4M/Pn	C5M/Pn	C6M/Pn
C1=albumin, C2=IgM/IgG, C3=cytokine/chemokines, C4=peroxiredoxin II, C5=C-reactive protein, C6=PaO ₂ /FiO ₂ , M=measurement, P=patient, D=donor and n=number						

Table 2

CP decision matrix.

Serological/protein biomarker criteria	C1	C2	C3	C4	C5
CPs					
CP 1					
	C1M/CP1	C2M/CP1	C3M/CP1	C4M/CP1	C5M/CP1
CP 2					
	C1M/CP2	C2M/CP2	C3M/CP2	C4M/CP2	C5M/CP2
⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮	⋮
CP n					
	C1M/CPn	C1M/CPn	C1M/CPn	C1M/CPn	C1M/CPn
C1=albumin, C2=IgM/IgG, C3=cytokine/chemokines, C4=peroxiredoxin II, C5=C-reactive protein, M=measurement, P=patient, CP=convalescent plasma and n=number					

criteria (i.e. serological/protein biomarker and/or PaO₂/FiO₂ criteria) is challenging because of the following issues.

Firstly, the patients should be prioritised on the basis of the severity of COVID-19, and the suitability of each CP should be evaluated on the basis of their value within each criterion. Secondly, different weights can be assigned for the mentioned criteria by decision-makers (i.e. specialists) and/or based on objective calculations, which further increases the complexity of the task. Thirdly, three criteria of serological/protein biomarkers and/or PaO₂/FiO₂ are considered benefit criteria, whereas the rest are considered cost criteria. Thus, the inverse relationship between serological/protein biomarker and/or PaO₂/FiO₂ criteria produces a trade-off. The prioritisation of patients with COVID-19 and/or CPs is a complex MCDM problem. The development of decision-making methods is important to preclude the prioritisation problem complexity [86–89].

3.2.2.2. Development of prioritisation approach via MCDM methods. This section proposes an MCDM approach with two important purposes. Firstly, weights are assigned to the serological/protein biomarker and PaO₂/FiO₂ criteria used in the prioritisation of CPs and COVID-19 patients. This stage aims to solve the issue of importance by investigating the most effectively used serological/protein biomarker and PaO₂/FiO₂ criteria for prioritisation. Secondly, CPs and patients with COVID-19 are prioritised on the basis of weighted criteria resulting from the first stage. This stage aims to eliminate two critical issues (i.e. multi-criteria and trade-off issues) through ranking alternatives (i.e. CPs and/or COVID-19 patients). Furthermore, many MCDM techniques are generally developed and used for weighting the evaluation criteria, alternative ranking or both. Alternative methods are ranked to determine the best approach [90,91]. Such techniques include weighted sum model [92], multiplicative exponential weighting [93], weighted product method [94], hierarchical adaptive weighting [95], simple additive weighting [96], technique for order of preference by similarity to ideal solution [97], vlskriterijumska optimizacija i kompromisno resenje [98], analytic hierarchy process (AHP) [99], novel

technique for the reorganisation of opinion order to interval levels (TROOIL) [49] and preference selection index (PSI) [100]. The major drawbacks of all of these methods, except for AHP, TROOIL and PSI, include the absence of weight generation provision [101–103].

Literature reviews have incorporated external weighting approaches to boost the efficiency of the original ranking strategies by generating the importance of many criteria in relation to the goal to avoid the abovementioned limitations [62,104,105,121]. Criterion weighting strategies allocate weights to attributes that are relatively important to one another [106,107]. However, weighting the evaluation criteria comprises two aspects. The first aspect indicates the importance of each criterion by conducting a pairwise comparison between the criteria set, which is called criterion weight [108]. The second aspect indicates that the importance of the criterion values is identified by the comparison process between the values of each criterion, which is called criterion value weight. For example, the PaO₂/FiO₂ ratio is the ratio of arterial oxygen partial pressure to fractional inspired oxygen. It is a widely used clinical indicator of hypoxaemia and can determine the level of respiratory distress in patients with COVID-19. Its weight of criterion value does not depend on the highest or lowest value but rather on the normal level of respiratory distress (200–300 as mild, 100–200 as moderate and below 100 as severe). In such cases, the pairwise comparison would be between the values of the PaO₂/FiO₂ criterion to specify the accepted value that the physician/medical staff considers as normal, which is called the value of the criteria.

In general, objective and subjective assessment methods have been developed to identify criterion weights. The objective methods use each criterion information to identify the criterion weight; such techniques include entropy and criterion importance through intercriteria correlation [109–111]. These techniques do not rely on a decision-maker's subjective judgement in weight assignment [112]. Weight is typically allocated directly to attributes via a mathematical method [113]. These techniques are widely used in previous works, and no inconsistency problem has been generated; however, subjective weight is the most significant in eval-

uating findings as it reflects the views and experiences of highly qualified experts [114]. When there is a need to assign weights for criteria subjectively, these approaches cannot incorporate decision-makers' knowledge and subjective value into one decision, which is the drawback of these techniques.

Subjective assessment provides weight to attributes on the basis of decision-makers' perceptions and subjective significance to each attribute. Subjective weights represent cumulative decision-makers' experience and subjective judgement in current decision-making scenarios [115]. Examples of these techniques are AHP and best-worst method (BWM) [116]. AHP is one of the most common methods used in multi-criteria decision-making. AHP depends on human preference [117]. This method was developed by Thomas L. Saaty. Despite its popularity, the method has a major drawback of inconsistency during criterion weighting. In AHP, the calculated priorities are plausible only if the pairwise comparison matrices have passed the consistency test. Furthermore, many decision problems cannot be structured hierarchically when the interaction of higher-level elements with lower-level elements and their dependency should be considered. In BWM, the weights of criteria are generated on the basis of pairwise comparisons between the set of criteria [107]. BWM is a new and important MCDM method that requires less pairwise comparisons than AHP; it derives the weights of criteria with high consistency. BWM was proposed by Rezaei in 2015; it can determine the weights of criteria on the basis of pairwise comparisons with a small number of comparisons (i.e. $2n-3$, where n is the number of criteria). Furthermore, BWM is better than AHP in terms of consistency. BWM executes reference comparisons, indicating that it only needs to determine the preference of the best criterion over all other criteria and the preference of all criteria over the worst criterion [61].

The benefits of few comparisons are the absence of the need to use fractional numbers and easier understanding by decision-makers (experts) compared with most MCDM methods. BWM utilises a 1–9 scale to perform pairwise comparisons. As mentioned above, BWM successfully reduces pairwise comparison from $n(n-1)/2$ in AHP to $2n-3$ in BWM. Similar to AHP, this method suffers from two issues, namely, the difficulty to determine the best and worst criteria and importance level of the best criterion over other criteria and the importance of all criteria over the worst criterion. In general, when the comparison uses a 1–9 scale, the decision-maker needs to state how many times a particular criterion is better than the other criteria. This comparison requires high cognitive power due to the unusual subjective comparisons. Thus, comparing two uncorrelated criteria is not a natural process and is difficult to achieve.

On the basis of viewpoints in the above discussion, the objective weighting approach computes the weight of the criteria without an inconsistency issue. However, it neglects human opinion, which is vital in making a proper decision. By contrast, the subjective weighting approach identifies the importance of criteria by computing the weight of each criterion. However, it faces an inconsistency issue. Both directions ignore the importance of the criterion value, which is essential in making correct and accurate rankings and selections. Therefore, to address the issues discussed above, this study proposes SODOSM, a novel MCDM method. This method can acquire the relative importance of various criteria with their values within CP and patient decision matrices objectively and subjectively without any inconsistency issue and provides a ranking for alternative CPs/patients.

3.2.2.3. Methodology of SODOSM. The proposed SODOSM behaviour comparison is conducted amongst each criterion within the CP decision matrix (i.e. albumin, IgM/IgG, cytokine/chemokines, peroxiredoxin II and C-reactive protein) and patient decision matrix (i.e. albumin, IgM/IgG, cytokine/chemokines, peroxiredoxin II, C-

Fig. 4. Procedure of SODOSM.

Table 3
Five-point Likert scale and equivalent scale number.

Number scoring scale	Linguistic scoring scale
1	No difference
2	Slight difference
3	Evident difference
4	Big difference
5	Huge difference

reactive protein and $\text{PaO}_2/\text{FiO}_2$) per alternative CP/patient to identify the worst solutions. This method can be divided into four steps, namely, data input, data transformation, linguistic data scale conversion and computation of the importance of criteria and ranking alternatives, as shown in Fig. 4. In SODOSM, an expert selects the worst value for each criterion and performs a reference comparison between the worst and the other values in the same criterion. An opinion matrix is then created. The opinion matrix is converted into equivalent Likert scale numbers (Table 3). The importance of any criterion is determined using objective weight. Lastly, a compromise technique is applied to achieve the final rank of alternative CPs/patients.

A Data input unit

The evaluation criteria are identified, and a scheme that re-lays goals is created. Evolving alternative schemes are used to reach the goals. Alternative patients and/or CPs are estimated in relation to the criteria of CP decision matrix (i.e. albumin, IgM/IgG, cytokine/chemokines, peroxiredoxin II and C-reactive protein) and the criteria of patient decision matrix (i.e. albumin, IgM/IgG, cytokine/chemokines, peroxiredoxin II, C-reactive protein and $\text{PaO}_2/\text{FiO}_2$). The decision matrix R is then created as follows:

Fig. 5. Reference comparison.

$$R = \begin{matrix} & c_1 & c_2 & \dots & c_n \\ \begin{matrix} A_1 \\ A_2 \\ \vdots \\ A_m \end{matrix} & \begin{bmatrix} v_{11} & v_{12} & \dots & v_{1n} \\ v_{21} & v_{22} & \dots & v_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ v_{m1} & v_{m2} & \dots & v_{mn} \end{bmatrix} \end{matrix} \quad (1)$$

A Data transformation

Upon the development of both decision matrices (the output of step A), the decision-makers (i.e. specialist) must select the worst solution from each decision matrix R for either CPs or patients. The worst solution is defined by three values, namely, max, min and critical values.

$$A_{\text{worst solution}} = \{(\max_i v_{ij}), (\min_j v_{ij}), Op_{ij}\} \times (v_{ij} | i \in j | j = 1, 2, 3, \dots, m), \quad (2)$$

where $\max_i$ represents the benefit criteria (i.e. albumin, IgM/IgG and $\text{PaO}_2/\text{FiO}_2$) amongst alternatives and $\min_j$ represents the cost criteria (cytokine/chemokines, peroxiredoxin II and C-reactive protein) amongst alternatives. These values are utilised to specify the worst solution relative to the benefit or cost criteria. Op_{ij} is the critical value of a worst solution but is neither a max value nor a min value. i and j represent the benefit and cost criteria, respectively. This step identifies the worst solution that is limited to the maximum and minimum on the basis of the benefit and cost criteria. Hence, the specialist has the flexibility to choose the worst outcome. After selecting the outcome, the worst solution and criteria per alternative are then compared (Fig. 5).

This step identifies distance measurements to the worst solution by applying the Euclidian distance of the actual values to the worst solution. The distance between the worst solution and alternative CPs and/or patients with COVID-19 is measured subjectively. Specialists are requested to assess if the criterion per alternative and the worst solution are significantly different. The comparison between the worst solution and criteria per alternative changes with the value of the linguistic term. Five scales are used in the comparison with the following linguistic terms: no differences, slight differences, evident differences, big differences and huge differences. Values V_{11} , V_{32} , V_{43} and V_{54} are nominated by specialists as the worst solution vector by using Eq. (2). Following the worst solution selection step, the worst solution and alternatives are compared using Eq. (3):

$$Op_{Lang} = \left\{ \left(\left(\tilde{v}_{ij} \otimes v_{ij} \mid j \in J \right), \mid i = 1, 2, 3, \dots, m \right) \right\}, \quad (3)$$

where $\otimes$ represents the reference comparison between the worst solution and alternatives (i.e. CPs and/or patients with COVID-19). The operator $\otimes$ uses the scale. This comparison is performed only for one column of decision matrix R (Fig. 6). Other columns use the same procedure to change the value of the linguistic term.

The specialist completes the comparison and then obtains opinion decision matrices (i.e. CPs and/or patients with COVID-19) by changing the value of each criterion with the specific comparison of the linguistic term expressed in Eq. (4) and demonstrated in Fig. 7. The final output of this block is the linguistic term opinion decision matrices (i.e. CPs and/or patients with COVID-19) that can be readily transformed into a five-point Likert scale to obtain a numerical opinion specialist. Furthermore, the problem of finding the weight of criterion value is solved by finding the weight implicit with the difference of achievement per criteria to the worst solution.

$$Op_{Lang} = \begin{matrix} A_1 \\ \vdots \\ A_m \end{matrix} \begin{bmatrix} op_{11} & \dots & op_{1n} \\ \vdots & \ddots & \vdots \\ op_{m1} & \dots & op_{mn} \end{bmatrix}. \quad (4)$$

A Convert the Likert linguistic scale into equivalent scale number

In this study, each recorded response made by an expert in the form of a Likert linguistic scale is converted into an equivalent scale number (Table 3).

The outcome of this step produces converted-opinion decision matrices (i.e. CPs and/or patients with COVID-19), which have values without any unit and with the same scale.

A Weighting criteria and ranking alternatives

The criterion weights are calculated objectively by an entropy process based on the measurement of uncertain data provided in both decision matrices (i.e. CPs and/or patients with COVID-19). This process immediately produces weights for a particular criterion on the basis of a reciprocal contrast between different criteria of variants for each criterion and then all of the criteria simultaneously. Objective criterion weights w_j are determined according to the entropy procedure in three steps.

• Calculation of information entropy

Information entropy is an important element for calculating criterion weight. High information entropy indicates that the information supplied by the criteria is increasing and that the weight is

Fig. 6. Comparisons between worst solution and criteria per alternative (i.e. CPs and/or patients with COVID-19 patients).

	c_1	c_2	c_3	c_4	c_5
A1	No difference	Big difference	Big difference	Slight difference	Huge difference
A2	Slight difference	Evident difference	Slight difference	Big difference	Evident difference
A3	Big difference	No difference	Evident difference	Evident difference	No difference
A4	Huge difference	Slight difference	Huge difference	No difference	Huge difference
A5	Evident difference	Huge difference	No difference	Huge difference	Slight difference

Fig. 7. Opinion decision matrices (i.e. CPs and/or COVID-19 patients).

large. The information entropy (e_i) is measured using Eq. (5):

$$e_j = - \frac{\sum_{i=1}^m f_{ij} \ln f_{ij}}{\ln m} \quad i = 1, 2, \dots, n, \quad (5)$$

where

$$f_{ij} = \frac{r_{ij}}{\sum_{i=1}^m r_{ij}} \quad \text{and} \quad 0 < e_j < 1. \quad (6)$$

If f_{ij} values are equal, then the entropy values of each criterion are maximum ($e_i = 1$). If f_{ij} is 0, then $f_{ij} \ln f_{ij}$ is 0 [118].

- **Computation of weight vector:** The weight of individual criterion (w_j) is calculated by the entropy process after calculating the information entropy. Eq. (7) expresses the significance of the criteria in the proposed method:

$$w_j = \frac{1 - e_j}{n - \sum_{i=1}^m e_j} \quad \text{where} \quad \sum_{j=1}^n w_j = 1, \quad (7)$$

where n is the number of criteria used. In this step, entropy process is employed on the alternative (i.e. patients and/or CPs) values per criterion to find the criterion weight.

- Computation of the rank of alternatives (i.e. patients and CPs)

After the criteria are weighted objectively by the entropy process, each criterion function is evaluated, and the measure of closeness is compared with the ideal solution. The compromise solution is the practical alternative that is nearest to the ideal solution and has a mutually concessional compromise [119]. Patients/CPs will be prioritised via the following steps:

Step I: Weighted decision matrices (i.e. CPs and/or COVID-19 patients) are defined as $[WM = \{wm_{ij}\}_{m \times n}]$ by applying Eq. (8):

$$wm = \sum_{j=1}^n r_{ij} w_j. \quad (8)$$

Step II: d^* and d^- are identified, where d^* is the maximum achievement for all alternatives (i.e. CPs and/or COVID-19 patients) in the WM per criteria and d^- is the minimum achievement for all alternatives (i.e. CPs and/or COVID-19 patients) in the WM per criteria. These values are determined using Eqs. (10) and (11), re-

spectively:

$$d^* = \max_j d_{ij}, \quad (9)$$

$$d^- = \min_j d_{ij}. \quad (10)$$

Step III: S and R are measured, where S is the summation the patient/CP values and R is the maximum value in those alternatives, by using Eqs. (12)–(14):

$$C_j = \{d^* - d_{ij}\} / \{d^* - d^-\}, \quad (11)$$

$$S = \sum C_j, \quad (12)$$

$$R = \max [C_j]. \quad (13)$$

Step IV: The final rank score (Q) is measured using Eq. (15).

$$Q = v(S_i - S^*) / (S^- - S^*) + (1 - v)(R_i - R^*) / (R^- - R^*), \quad (14)$$

where v is introduced for the strategy of maximum group utility and $(1 - v)$ is the weight of the individual regret. The value for v is 0.5. However, any v value can be assigned to the 0–1 range. $S^- = \max S_i$, $S^* = \min S_i$, $R^- = \max R_i$ and $R^* = \min R_i$. The patients/CPs with the lowest Q value are the best alternatives.

Step V: The patients/CPs are ranked in ascending order by sorting the results from Q . Finally, the set of alternatives (CPs/patients) is ranked by their score in ascending order. A low mean value indicates a high priority rank.

The limitation of this study is that the proposed framework has not been tested on infected cases due to the lockdown and global pandemic outbreak. Collecting real datasets of patients with COVID-19 and donors who have already recovered is difficult.

4. Conclusion

The COVID-19 pandemic has caused an unmatched human and health crisis [120]. The virus can be eliminated by improving the healthcare quality of patients with COVID-19 and providing them with protective antibodies from the blood of patients who have recovered from this disease. This procedure could theoretically help boost the immunity of infected patients. To help doctors accelerate treatments, this study presents an intelligent rescue framework for the transfusion of appropriate tested CPs to the most severe COVID-19 cases on the basis of biological requirements. A detailed description of the proposed framework has been discussed sequentially in two phases. Moreover, several MCDM methods have been debated and analysed in terms of their capability in the adoption. These methods are utilised in the proposed framework. However, given their limitations, a novel MCDM method called SODOSM is proposed to assign the comparative importance for the criteria used in both decision matrices proposed (i.e. CPs and patients with COVID-19) and then prioritise CPs/patients effectively. This study presents seven recommendations for future work. Firstly, the proposed framework will be implemented and tested to serve and help the healthcare sector in fighting the SARS-CoV-2 virus by improving the immunity of infected patients. Secondly, the proposed framework can be used with any future generation of coronaviruses or other new viruses to rescue the newly infected patients based on the drawn strategies of this framework. Thirdly, big data life cycle stages (i.e. collection of data, cleaning of data, classification of data modelling and its delivery) of the prioritisation process for donors and patients with COVID-19 will be discussed in detail. Fourthly, the possibility of adoption of the internet of things in the prioritisation process of COVID-19 patients will be investigated. Fifthly, the proposed framework can be run and performed in the indoor/outdoor hospitals over a telemedicine environment to rescue a huge number of patients widely. Such

a process can be provided in two different architectures, namely, centralised telemedicine based on data centre and decentralised telemedicine based on blockchain technology. In this line, the privacy and security of patients'/donors' information will be provided in addition to the network security of telemedicine architectures. Sixthly, the proposed framework can be helped the administrative divisions of the healthcare organisation make the correct judgement/decision in choosing a proper ML hierarchical and/or multilabelled classification method for COVID-19 on the basis of the proposed SODOSM method. Seventhly, if needed, the proposed SODOSM can be extended to fuzzy and/or rough environments to manage uncertainty and ambiguous problems.

Declaration of Competing Interest

None

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