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Age prediction from COVID-19 blood test for ensuring robust artificial intelligence

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ABSTRACT

With the advancement of artificial intelligence (AI) nowadays, the world is experiencing conveniences in automating some complex and tedious tasks, such as analysing large data and predicting the future by mimicking human expertise. AI has also shown promise for mitigating future crisis, such as pandemic. Since the beginning of the COVID-19, several AI models have been published by the researchers to help the healthcare to fight in this situation. However, before deploying the model, one needs to ensure that the model is robust and safe to learn from the real environment, especially in medical domain, where the uncertainty and incomplete information are not unusual. In the effort of providing robust AI, we proposed to use patient age as one of the feasible feature for ensuring vigorous AI models from electronic health record. We conducted several experiment with 28 blood test items and radiologist report from 1,000 COVID-19 patients. Our result shows that with the predicted age as an additional feature in mortality classification task, the model is significantly improved when compared to adding the actual age. We also reported our findings regarding the predicted age in the dataset.

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1. INTRODUCTION

Artificial intelligence (AI) has been helping humanity since the beginning of the neural network era. It continues to contribute in an era where the deep learning (DL) approach became very popular in the 2010s. AI has become a rising field that revolutionary produces solutions to automate many tasks in several domains, including healthcare. Scientists have developed promising models that have the potential to reshape the healthcare domain, especially in the settings where resources are lacking, such as in the coronavirus disease 2019 (COVID-19) pandemic situation. In this kind of situations, health workers often feel exhausted when dealing with the rapidly increasing number of patients. AI researchers have been proposing many solutions for this, including automatic diagnosing, severity, and mortality prediction. Several studies on how AI can help COVID-19 have been published. From Scopus indexed database, there were 1,667 documents returned for the keyword "AI for COVID-19", published in 2020 to 2022.

This advancement of AI technology has also been encouraged to be deployed in high-stakes settings, such as autonomous driving and managing power-grid. Such applications have been raising another need of a robust AI [1]. Before deploying the model, one needs to ensure that the model is robust and safe to learn

from the real environment, where the uncertainty and incomplete information exist. According to Dietterich [1], robust AI can be achieved through several ways; such as robust optimization, regularization in machine learning (ML), modify the objectives to be risk-sensitive, robust inference, detecting model failures, causal models, ensemble method, and expand the model (such as knowledge model employed by Google that contains millions of objects and relationships).

Several AI models have been developed for COVID-19 problem, since the first time this disease was detected in Wuhan, China, 2019. For diagnosing task, the standard test use for detecting COVID-19 is through reverse transcription polymerase chain reaction (RT-PCR) test. The presence of this disease can also be confirmed from the patients' radiology test result chest X-ray (CXR) and computerized tomography (CT) scan. The first method, RT-PCR, is more preferable because its speed and accuracy [2]. However, the specificity and sensitivity of this method have a fairly large gap between one test kit and another. According to WHO, the 'acceptable' test method can have the sensitivity above 80% and specificity above 90%, while the 'desired' test method can have sensitivity above 90% and specificity above 99% [3]. Other that that, the RT-PCR test also has several limitation to be used in large-scale diagnosis, such as the long turnaround times (over 2-3 hours), certified laboratories, trained healthcare staff, expensive equipment and reagents which possibly will make the demand overcome supply [4]. Other than radiology images, blood test can also be used as the alternative method for initial patient screening. When compared to the gold standard of RT-PCR method, this routine blood test will usually can be delivered more quickly with a hematology analyzer within 30 minutes to 2 hours time range, as mentioned in [2]. Therefore, in the medical domain itself, some researchers have also considered the blood test for COVID-19 diagnosis such as [5]. Following this fact, the researchers in AI domain, also developed several models to diagnose COVID-19 from blood test data, such as the one in [2], [6]-[11]. In addition to the diagnosis task, the blood test exam is also used to predict the severity of the disease [12] and mortality [13], [14].

As suggested by Dietterich [1], we need to perform additional efforts for implementing a robust AI, before the models can be deployed in real-world settings. There are several ways to ensure the robustness of the AI models in medical domains. One effort has shown by removing bias in radiology image classification [15]. The main contribution of this paper is proposing a novel way to handle this problem by using "age" as the important feature to ensure the robustness and reliability model. The patient's age, as one additionalan important features that can improve and check the consistency of the results of the AI model of blood tests for COVID-19 patients, was chosen because of some reasons as follows: i) age is a risk factor for almost all chronic disease, ii) knowing the patient's age for planning proper triage is important, iii) in forensic and anthropological investigations, predicting age is common method, and iv) age was found as one of the most significant contributors of predicting mortality and diagnosing COVID-19.

As stated in [16], the rates of disease in each age group are different. Age is a risk factor for almost all chronic disease, including most cancers. In the epidemiology, the age is also important factor to observe the findings in collecting health statistics from the communities. The epidemiologist refer this as age-adjustment, where it allows the statisticians to give different weight for people from different age group to remove the confounding factor.

Knowing the patient's age for planning proper triage is important. Not only that, knowing the patient's age also shows benefits in establishing a diagnosis, such as the study conducted by Urban *et al.* [17]. They confirm that age specific cut off point of D-Dimer can significantly improve the specificity of the venous thromboembolism (VTE) diagnosis in a patient, particularly for older age. They compared the result with the conventional D-Dimer cut off point.

Similar study which focus on predicting the patients' age has been carried out by Wang *et al.* [18]. They proposed a model that can predict the chronological age of patients from electronic medical records (EMR) which contains information about the patient physiological state: vital signs and lab tests. They aim to identify the discrepancy between chronological and physiological age of patients which is vital for preventative and personalized care. They trained a DL model and the result is satisfied with the standard deviation error of 7 years.

In forensic and anthropological investigations, predicting individual age is not new. A recent study by Karargyris *et al.* [19] demonstrated a novel approach of predicting age automatically by using DL model from medical images. Based on their study, various medical imaging modalities often contain individual visual features of a person. The benefits of their research are not only can be used for forensic purposes, but can also be used for planning appropriate treatment, for example, for children who are detected to have growth disorders

from bone age prediction.

Several studies also confirm that age was one of the most significant contributors of predicting mortality in COVID-19. One study that confirms this findings has been conducted by Ruan *et al.* [20]. Based on their trial, age was found to be significant along with the presence of comorbidity disease, secondary infection and inflammation in the blood. Another similar study in New York City by Vaid *et al.* [21] also confirms the same result. They stated that at 7 days, age was found to be important for COVID-19 mortality with rapid increase of feature associated with increasing age. A study by Brinati *et al.* [10] also found similar findings saying that age was one of the top-10 most important feature in diagnosing COVID-19.

On the other hand, in this digital era when every patient history record is stored electronically, it is also necessary to develop a system that can confirm the patient's age based on their laboratory readings. This is especially useful when the patient age data is missing due to human error or other unexpected oversight when entering data. Therefore, a system to confirm the patient's biological age is needed, to develop appropriate triage and make correct treatment decisions. In a pandemic situation like now, people find it useful to use telemedicine to seek first aid from a healthcare practitioner. Telemedicine is also a digital technology that is currently very popular during this pandemic. This mechanism will be useful when there is a need for the patients need to send the blood test result and consult with the doctors remotely through telemedicine.

This study is conducted based on our previous findings on training the AI models to predict patients' age from CXR [22] and blood test data [23]. For the radiology image, the models ware trained on predicting age from general case of CXR, while for the blood test, the models were trained on both COVID-19 and non-COVID-19 case. However, since our finding in [23] shows that for the blood test data, COVID-19 dataset performed better than the other dataset (Pneumonia and other disease), in this paper, we want to focus on the COVID-19 blood test dataset.

This paper is limiting the scope of the research to only focus on the patient's with COVID-19, as people diagnosed with this disease have a particular biological markers and a set of tests. Therefore, the results obtained from the conclusions of this research will be easier to be applied. We conducted several experiments, where it can be composed into two big scopes: predicting age from blood test and predicting mortality from blood test by considering age as a feature. In the first scope, we want to show the impact of radiologist observation text report to predict age from blood test. In the second scope, we performed experiments by involving the actual age and predicted age with each of the blood test items in predicting the mortality of the patients.

2. RESEARCH METHODOLOGY

This section will show about the research methodology used in the paper. The research work flow is shown in Figure 1. The process started from data collection, then it was followed by preprocessing step, dividing the data into training and testing, then perform several experiments and evaluation. As explained in the previous section, this study composed of two big tasks, namely predicting age and predicting mortality. For each task, we conducted experiments and tuned two models. Hence, we ended up with four AI models. The summary of the four models is shown in Table 1.

2.1. Dataset and preprocessing

In Figure 1, the four AI models were highlighted in yellow boxes, they are: i) model for predicting age; ii) model for predicting age with radiologist report as extra feature; iii) model for predicting mortality with actual age; and iv) model for predicting mortality with predicted age. As shown in Figure 1, the first step in this study was collecting data. The data was collected from a COVID-19 referral hospital, Pasar Minggu Regional Hospital in Jakarta, Indonesia, during the first wave of the pandemic, March to December 2020. There were 1,000 patients records collected as a sample in this study. Each patient was administered to several blood test examination during their stay in the hospital. Consequently, the data contains several rows of blood test result from each patient. So in total, we have 24,629 records in the dataset. The data collected in this study include: patients age, blood test, mortality status, and radiologist report (sample is provided in Figure 2).

The radiologist report were given as an extra information about the patient conditions, in replace of the radiology images. This is due to the hospital policy, where the radiology images cannot be sent out to external parties. We plan to conduct deeper analysis of this additional feature in another paper. For this study, we use this extra feature to examine whether there is improvement in the performance when compared to only using the blood test data.

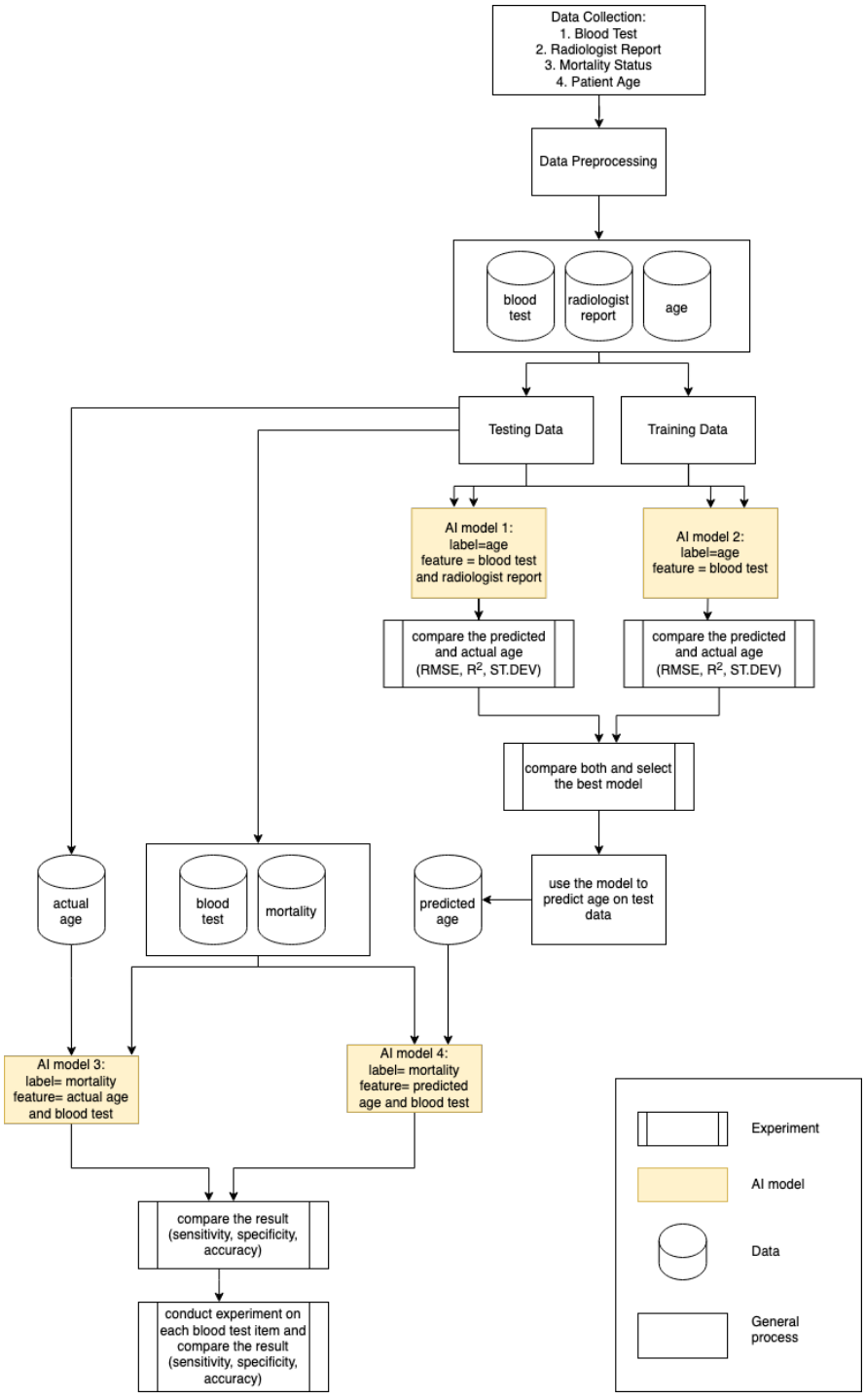

Figure 1. Research flow diagram

Table 1. Summary of the four AI models

Model	Task	Predicted value/label	Feature	Evaluation
1	regression	age	28 blood test item	Normalised RMSE and R^2
2	regression	age	28 blood test item and radiologist report	Normalised RMSE and R^2
3	classification	mortality	each blood test item and actual age	specificity, sensitivity, accuracy, F1-score
4	classification	mortality	each blood test item and predicted age	specificity, sensitivity, accuracy, F1-score

Original report in Bahasa

```
Thorax PA
Perbandingan : foto thorax PA tanggal 07-01-2018
Cor sedikit membesar ke lateral kiri dengan apeks yang tertanam
pada diafragma, pinggang jantung normal (CTR 52%).
Sinuses dan diafragma normal.
Pulmo:
    -Hili normal.
    -Corakan bronkovaskuler normal.
    -Tampak infiltrat di tengah sampai bawah kiri.
    -Kranialisasi (-).
KESAN :
    -Kardiomegali ringan.
    -Infiltrat di tengah sampai bawah kiri dd/ bronkopneumonia.
    (dibandingkan dengan foto thorax PA tanggal 07-01-2018 : stqa)
```

Translated report in English

```
Thorax PA
Comparison: PA thorax photo on 07-01-2018
Slightly enlarged left lateral with embedded apex
on the diaphragm, the waist of the heart was normal (CTR 52%).
The sinuses and diaphragm are normal.
Pulmo:
    -Normal hila.
    -Normal bronchovascular pattern.
    -Looks infiltrate in the middle to the bottom left.
    -Cranialization (-).
IMPRESSION:
    -Mild cardiomegaly.
    -Infiltrate in the middle to bottom left chest/ bronchopneumonia.
    (compared to PA thorax photo on 07-01-2018: status quante)
```

Figure 2. A sample of radiologist report dataset

Based on our interview with the pulmonologist from the hospital and also considering our previous findings in [14], we decided to use only 28 blood biomarkers. These biomarkers is shown in Table 2. From the the patients' age data, it was varied from the youngest, 1.5 years old, to the oldest, and 92 years old. The histogram of age with the proportion of each patient outcome is shown in Figure 3. It is shown that the patient's age ranging from 1.5 years old to 92 years old, with two peak points in between 36 and 41 years old, also between 56 and 61 years old. While the distribution of the dead outcome only have one peak point, that is in between 56-61 years old.

For preprocessing step, we employed backward fill and k-nearest neighbour (KNN) imputation technique. The first method is to fill the missing values of the blood test with the latest exam result. Then, KNN technique is used for final step in imputation to clean the whole dataset. KNN works by finding the similar values and estimate the missing one. To handle the imbalanced dataset in mortality, where the dead status is much lower than the survive one, we used SMOTE technique to perform data upsampling for minority class. We divided the dataset into 60:40 proportion for training and testing. We also ensure that when splitting the dataset into training and testing, there was no data belong to the same patients were split up.

2.2. Text embedding technique

In this section, we will explain the text embedding technique for preparing the radiologist report data. In our experiment, we only used FastText [24], a library created by Facebook Research team for efficient text classification and representation learning. The library already provided the pre-trained word vectors for Indonesian languages, which were trained on Common Crawl and Wikipedia. This word vectors model were trained by Grave *et al.* [25], and published in 2018. The reason we chose this library in our experiment, other than the reason that they provided Indonesian language model, they also offer several benefits over the other library such as word2vec, gensim or glove, i.e. they use assumption that a word is formed by a n-grams of character. This can be helpful to find the vector representation of a rare word. It can also give vector representation, even when there is no existing word in the dictionary. Since our radiologist report dataset contains so many rare word, which are specific on the pulmonary domain, the FastText library is mostly suitable. Several latest studies already showed evidence that FastText performed better than the other libraries,

such as the one performed by Alghamdi and Assiri [26]. The other study also showed that FastText not only performed better but also faster [27].

Table 2. Biomarkers used in blood test dataset

Biomarker	Feature code	Normal level (adult)	Unit
HEMATOLOGY			
Hemoglobin	HB	13.2 - 17.3	g/dL
Hematocrit	HCT	40 - 52	%
Leukocytes	LEKO	3.8 - 10.6	$10^3/\mu L$
Platelets	PLT	150 - 440	$10^3/\mu L$
Erythrocytes	ERI	4.40 - 5.90	$10^6/\mu L$
Red cell distribution width	RDW	11.8 - 14.5	%
AVERAGE ERYTHROCYTE VALUE			
Mean corpuscular volume	MCV	80 - 100	fl
Mean corpuscular hemoglobin	MCH	27.5 - 33.2	pg
Mean corpuscular hemoglobin concentration	MCHC	32 - 36	g/dL
COUNT TYPE			
Basophils	BASOFIL	0.0 - 1.0	%
Eosinophils	EOS	1.0 - 5.0	%
Stem neutrophils	NEUTB	3.0 - 5.0	%
Segmented neutrophils	SEGMEN	50 - 70	%
Lymphocytes	LIMFOSIT	25 - 50	%
Monocytes	MONOSIT	2.0 - 8.0	%
Neutrophil-lymphocyte ratio	NLR1	<3.12	
Erythrocyte sedimentation rate	LED	0 - 20	mm/hour
HEMOSTASIS			
D-Dimer	DDIMER	<0.5	$\mu g/mL$
prothrombin time	PTHSL	10.80 - 14.40	second
Activated partial Thromboplastin Time	APTTHSL	25.00 - 35.00	second
BLOOD CHEMISTRY			
Arterial blood gas analysis			
Partial pressure of oxygen	PO2_N	71.0 - 104.0	mmHg
Oxygen saturation	O2S_N	94.0 - 100.0	%
Liver function			
Serum glutamic oxaloacetic transaminase	SGOT	<50	U/L
Serum glutamic pyruvic transaminase	SGPT	<50	U/L
Diabetes			
Random plasma glucose test	GDSFULL	70 - 180	mg/dL
Kidney function			
Urea	UREUM	<48	mg/dl
Creatinine	CREAT	0.70 - 1.30	mg/dL
Cardiac enzymes			
Lactate dehydrogenase	LDH	50 - 150	U/L

In order to transform the radiologist text report to vector representation, so that the feature can be used in training the model for solving predicting age problem, we used a method called *get_sentence_vector()*. It gets the vector of a sentence with the size of 300 for each sentence, by averaging the L2 norm of word vector or n-gram embeddings by element-wise [28]. In order to get the sentence vector, we performed the following preprocessing step for each row in the radiologist dataset:

- remove all the special character, including the newline,
- calculate the sentence vector representation by using method `get_sentence_vector()`,
- we obtained the vector with the length of 300, and
- we summed up all those 300 elements inside the vector to get a single numerical representation for each data. For example, for the text shown in Figure 2, the resulting vector is -0.74.

2.3. Model training and parameter

For all the four AI models, we only use the XGBoost algorithm [29], which is a tree based ensemble ML algorithm. We decided to use this algorithm after observing that in several experiment, such as the one we performed in [23], our data works best with XGBoost model. The only parameter that has been tuned for both age and mortality prediction task is the maximum depth, which is 20 (the default is 3), while for the rest of the parameters were left with their default value. The maximum depth was chosen because based on our experiment, there is no improvement for the model training performance after the depth of 20. With this depth,

a single experiment took only about 15 seconds in Google Colab (24,629 of total rows and 29 columns were trained), which is still a reasonable performance. Based on the result from several experiments there was no significant improvement has shown by tuning the other parameters. Hence, we decided to focus on the maximum depth parameter.

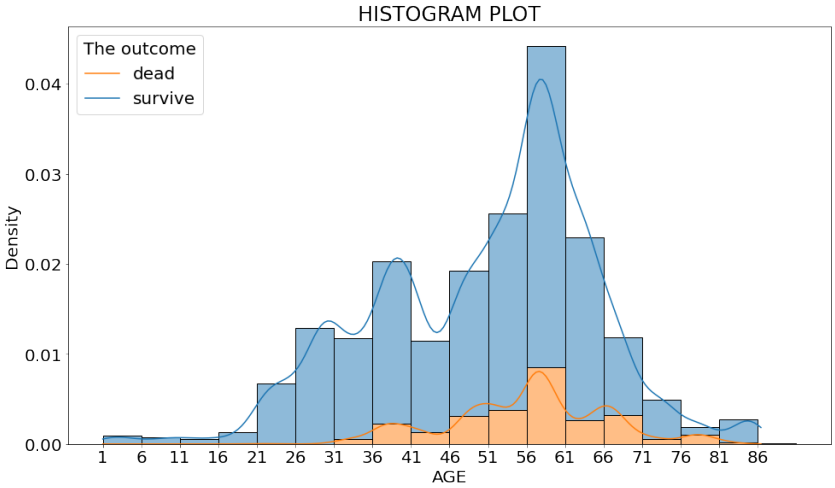

Figure 3. Histogram of patient's age and outcome

2.4. Evaluation technique

The dataset were split into 60:40 proportion, where the training is 60% and the testing portion is 40%. The split point is based on the patient ID to ensure that there is no blood test record of a patient is separated between training and test data. This setting is chosen due to the number of blood test record that were not the same for all patients. We tried to split into different proportion, such as 70:30 and 80:20, however, in some round of experiments, we were only left with very few samples in the test set and it causes bias when calculating the model's performance.

We performed two tasks of ML in this study, they are: regression (for age prediction) and classification (for mortality prediction). For the regression task, we used two metrics called normalised root mean squared error (NRMSE) and coefficient of determination (R^2). The NRMSE is the normalised version of RMSE, which is to measure the differences between the predicted value and the observed value. We use NRMSE instead of the RMSE because it is easier to compare the models of different scale. NRMSE is often expressed as a percentage, where low value indicates better performance because of the less residual.

The other metric, is called coefficient of determination (R^2). In ML regression task, this metric can be used to measure the performance of the model by calculating the proportion of the observed value that is predictable. For the second task, mortality prediction with classification, we used four common metrics, namely sensitivity, specificity, accuracy, and F1-score.

3. RESULT AND DISCUSSION

3.1. Predicting age from blood test

In this part, we reported the evaluation result of AI model 1 and AI model 2 as shown in Figure 1. The additional feature, radiologist report did not show adding any significance improvement to the model. We repeated the experiment 100 times, and the Mann Whitney U Test for two independent samples only shows the p-value of 0.1 (greater than threshold of alpha 0.05). The result from both models was quite similar. We show the result of the model with radiologist report in Figure 4. The R^2 is shown in the figure as high as 33% of the variable can be explained by the other variable. While the Pearson coefficient r value shows there is positive correlation between the predicted age and true age (> 0.5).

However, when we observed the feature importance, the radiologist report was always in the top 5 of the important features to the model. We show the plot of both true age and predicted age distribution in

Figure 5. It shows that our model can predict the same highest peak as the true age, that is in between 56 and 61 years old. The figure shows that the distribution of predicted age is quite similar with the true age. The overlapped bar (purple shaded color) shows there is same amount of data in the particular bin.

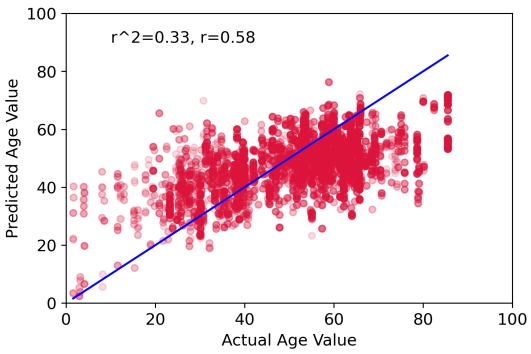

Figure 4. Scatter plot of true age and predicted age

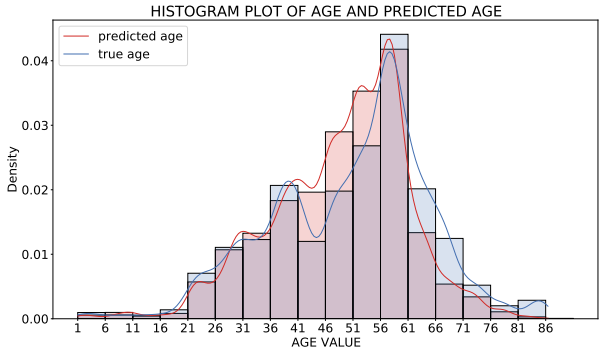

Figure 5. Distribution of predicted age in comparison with true age

3.2. Enhancing the blood test with age for mortality prediction

3.2.1. Correlation matrix

The correlation matrix of the top-15 features in the dataset is shown in Figure 6. The darker color shows the higher correlation. Several blood item have relatively high correlation with both actual and predicted age, such as SEGMEN, UREUM, MCH, MCV, and LED. The UREUM has higher correlation with the predicted age than the actual age. Both true age and predicted age, agree on the correlation with other features, however, the predicted age have slightly higher correlation score.

3.2.2. Mortality proportion in predicted age

We explore the proportion of the actual died patient in each age range. The result is shown in Figure 7. From each bar show in the figure, the predicted age capture more died patient in the older range, i.e. older than 70 years old. With this result, we can say that one cannot use the age alone as an easy factor to predict the mortality. In the actual age, patients with bin age 75, who actually died is only 35.86%, while our predicted age actually can capture 53.50%. The red bar shows the dead status, and the yellow bar shows the survive status. The proportion of dead outcome in predicted age (top figure) is higher when compared to the true age for the age older than 70 years old, with the exception of 85 years old age bin where the percentage is not high in the dataset.

3.2.3. Adding predicted age as additional feature

In this part, we reported the result of comparing AI model 3 and AI model 4 as shown in Figure 1. We run an experiment by using each blood feature and add the result of the predicted age as the additional feature to classify the mortality outcome for each patient. Our result show that this predicted age can increase the performance of the model in the 18 blood items. We repeated the experiment 30 times and compared the result with the one that added with the true age. We measure all the accuracy, sensitivity, specificity and F1-score and calculate the p-value to determine whether adding predicted age is significantly better than adding true age to predict the mortality. The result of the blood items which shows the significance result (p-value < 0.05) by adding the predicted age is shown in Table 3. From the table we can see that all the classification measurement return very good result, except the sensitivity. This is due to the limited case of mortality in our dataset which is very low when compared to the survived case.

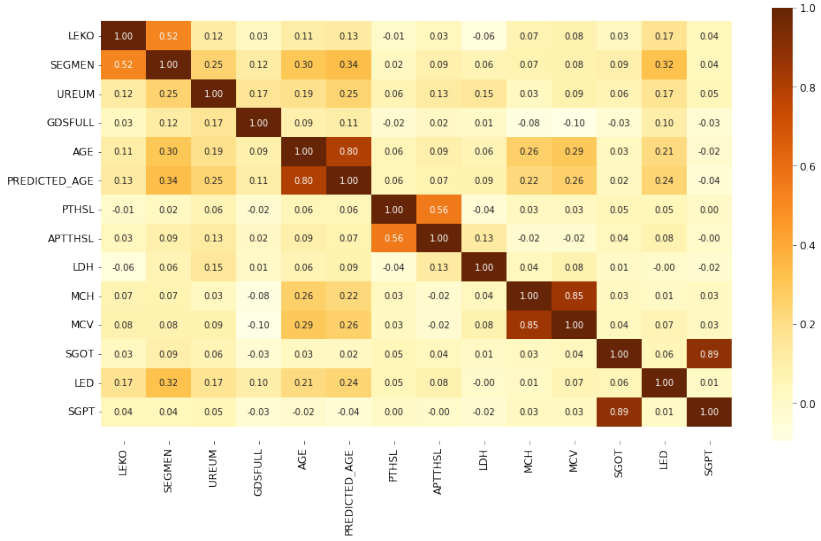

Figure 6. Correlation matrix of the top 15 features for mortality

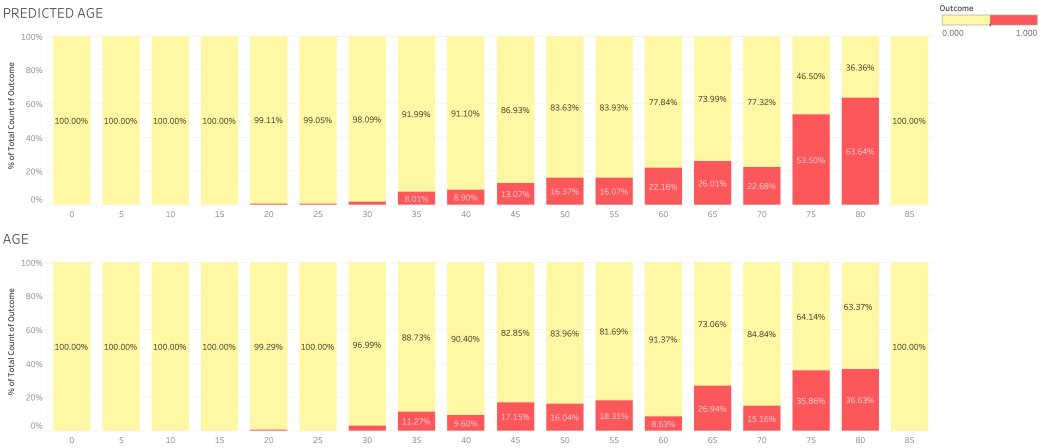

Figure 7. Predicted age vs true age in predicting mortality

Table 3. List of blood items which shows significant difference after adding predicted age

Blood Item	Accuracy	Sensitivity	Specificity	F1
HCT	0.82	0.30	0.87	0.84
ERI	0.79	0.30	0.84	0.82
RDW	0.80	0.28	0.85	0.83
MCHC	0.85	0.25	0.91	0.86
MONOSIT	0.86	0.35	0.91	0.87
NLR1	0.83	0.44	0.86	0.85
APTTHSL	0.80	0.36	0.84	0.83
PO2_N	0.82	0.40	0.86	0.85
O2S_N	0.80	0.32	0.84	0.83
DDIMER	0.82	0.30	0.87	0.84
LEKO	0.80	0.35	0.84	0.83
MCH	0.86	0.27	0.91	0.86
SGOT	0.85	0.48	0.88	0.87
SGPT	0.82	0.41	0.86	0.85
PTHSL	0.80	0.37	0.84	0.83
LIMFOSIT	0.84	0.43	0.88	0.86
GDSFULL	0.80	0.37	0.84	0.83

4. CONCLUSION

The study of predicting patient age is still limited. We explore several reason on why this is needed when we have to deal with AI model. Not only showing an effort to produce a robust AI model, but also to improve the performance of the model itself. In this study, we show the importance of predicting age from patient laboratory result. We conducted several experiments and show the pipeline of how the ML can predict age from the given dataset. Our result shows that with the predicted age as an additional feature in mortality classification task, the model is significantly improved when compared to adding the actual age. In the future, we want to explore more about combining the other patient electronic health record and try the other ML algorithm.

ETHICAL CLEARANCE

The patients' medical records used in this study were collected by the data provider, including epidemiological, demographic, clinical, laboratory and mortality outcome information. This study has been approved by the Ethics Committee of the data provider, Pasar Minggu Regional Hospital Jakarta, Indonesia. The requirement for patient consent was waived as this was a secondary analysis of anonymized data.

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