CLINICAL UPDATES IN COVID-19

COVID-19 Mortality Review in Malaysia & Updates on Clinical Management of COVID-19

INSTITUTE FOR CLINICAL RESEARCH, NIH MY

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Published by Institute for Clinical Research, NIH MY, 2020.

COVID-19 MORTALITY REVIEW IN MALAYSIA & UPDATES ON CLINICAL MANAGEMENT OF COVID-19
First edition. June 23, 2020.

ISBN: 9780463561461
DOI: 10.5281/zenodo.3903972

Front cover photo: Photo taken on 15 October 2014 during simulation exercise by Chew Cheng Hoon. Front cover design by Chew Cheng Hoon.

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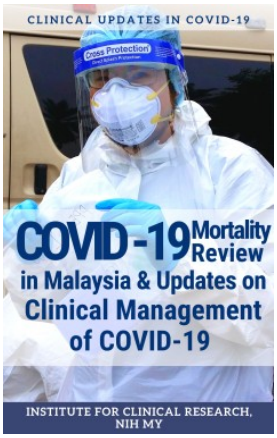

COVID-19 Mortality Review in Malaysia & Updates on Clinical Management of COVID-19

Disclaimer

- This transcript was prepared based on the Clinical Updates in COVID-19 live webinar session on 18/06/2020. The panellists for this webinar are Dr.Suresh Kumar Chidambaram and Dr.Faizah Muhamad Zin.
- The transcript was prepared by Ms.Yip Yan Yee, Mdm Lim Ming Tsuey and Dr. Chew Cheng Hoon from Institute for Clinical Research, NIH Malaysia.
- This is intended to share within healthcare professionals, not for the public.

Citation:
Chew, C.H., Yip, Y.Y., Lim, M.T., Suresh, K.C, Faizah, M.Z., Lee, C.K.C., & Goh, P.P. (2020). COVID-19 Mortality Review in Malaysia & Updates on Clinical Management of COVID-19: Clinical Updates in COVID-19. Kuala Lumpur, Malaysia: Institute For Clinical Research, NIH
DOI: 10.5281/zenodo.3903972

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"COVID-19 Mortality Review in Malaysia" by Dr. Faizah Muhamad Zin, Medical Development Division, MOH

Introduction

Outlines

Background

How do we do it?

1. Could you talk about drug therapy in COVID-19, namely about the withdrawn paper on hydroxychloroquine (Lancet) and the usage of dexamethasone? Initially WHO has advised us not to use steroids upfront. What is your comment on this?

2. In the previous webinar, it was mentioned that adolescents are more likely to have Kawasaki Disease like illness (MIS-C). Do we see such characteristics among patients older than 12 years old and young adults?

3. We know that in the later part of our national COVID-19 mortality committee, we brought in forensic colleagues to help the committee. Dr.Faizah, can you share with us, (clearly we are not doing post-mortem for every case), going forward, what is the game plan for the Ministry of Health in terms of when do we do post-mortem among COVID-19 cases who may passed away in the future?

4. What is your comment of the types of COVID-19 in South East Asia based on Cambridge scientists?

5. Are there any COVID-19 cases in Malaysia or abroad that affect patients with haemoglobinopathies such as thalassaemia or sickle cell?

6. What is the panellists' view on using hydroxychloroquine (HCQ) at an early stage of COVID-19 infection that might reduce the severity of COVID-19 patients? WHO withdrew HCQ arm.

7. What is your opinion on WHO withdrawing the recruitment of patients for hydroxychloroquine treatment in trial?

8. We hope there is no second surge of COVID-19, but as DG of Health has mentioned many times, we are preparing for any possibilities. In terms of the clinical setup, will there be a change in the way we set up our clinical services for COVID-19? As you know there are some COVID-19 hospitals like Sungai Buloh Hospital, and we have hybrid hospitals. Going forward, will there be change in how we deal with COVID-19 in the future, in terms of health care delivery?

9. We are all happy to see the data on COVID-19 patients' recovery using dexamethasone, as it is easy accessed to. Obviously, tocilizumab also has good data

coming forward. Are you aware of any studies which compare these two drugs head-to-head?

10. Are patients on Disease-modifying anti-rheumatic drugs (DMARDs) and long term steroids less likely to get cytokine release syndrome?

11. What are the mortality numbers involving healthcare workers?

12. Are we going to use convalescent plasma in Malaysia?

13. Can you update us on the sequencing of the virus strains? Were there mutations? Will it affect the pick up rate of RT-PCR? Any updates from the Institute for Medical Research (IMR)?

14. What are the common pitfalls that we picked up from the mortality review?

15. Could you comment on the false positives on RT-PCR testing?

"Wrap Up Message" by Datuk Dr Christopher Lee

Speakers' Brief Bio

"Updates on Clinical Management of COVID-19" by Dr. Suresh Kumar, Hospital Sungai Buloh

Thank you, Dr. Chris. I think as Dr. Chris has mentioned that we had quite a few changes in COVID-19 management. We thought it's time for us to give an update on what we think currently the way COVID-19 should be managed.

Clinical Staging of Syndrome Associated With COVID-19

This is how we have been classifying it in Malaysia. For example, category 1 which is asymptomatic down to category 5 that is critically ill multi-organ involvement. Many of the things that I will talk about are related to these clinical categories. You can group category 1 to 3 as mild because they are the ones who do not require oxygen at all while category 4 and 5 are the ones that require supplemental oxygen or ventilation. That's how we divide our clinical categories.

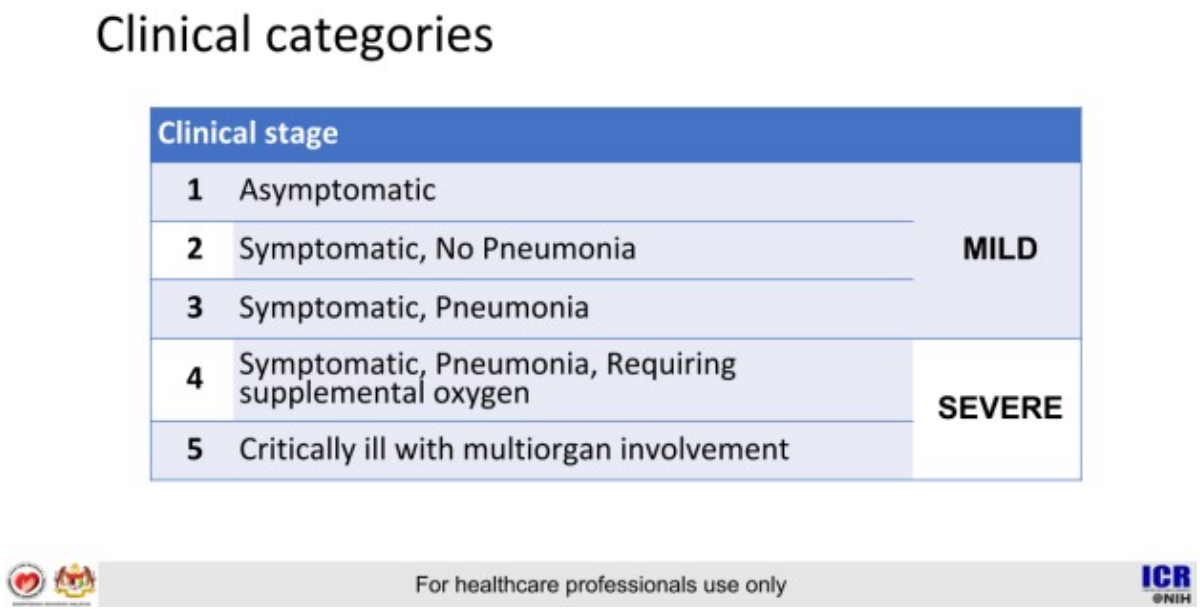


Diagram 1: Clinical staging of Syndrome Associated With COVID-19

National COVID-19 patients: Age group vs worst case classification

This is the data we have with the Institute for Clinical Research, Clinical Research Centre (CRC) and the rest of the centres in the country. We managed to put in about 3600 patients into a database currently. This is a spread of the cases that you can see. Majority of the cases are mild cases and the number of severe cases are smaller. Majority of the cases that we have seen in our country are mild, category 1, 2 and 3 and a small number are severe. This is to give you an idea of what proportions are mild and what proportions are severe in the country.

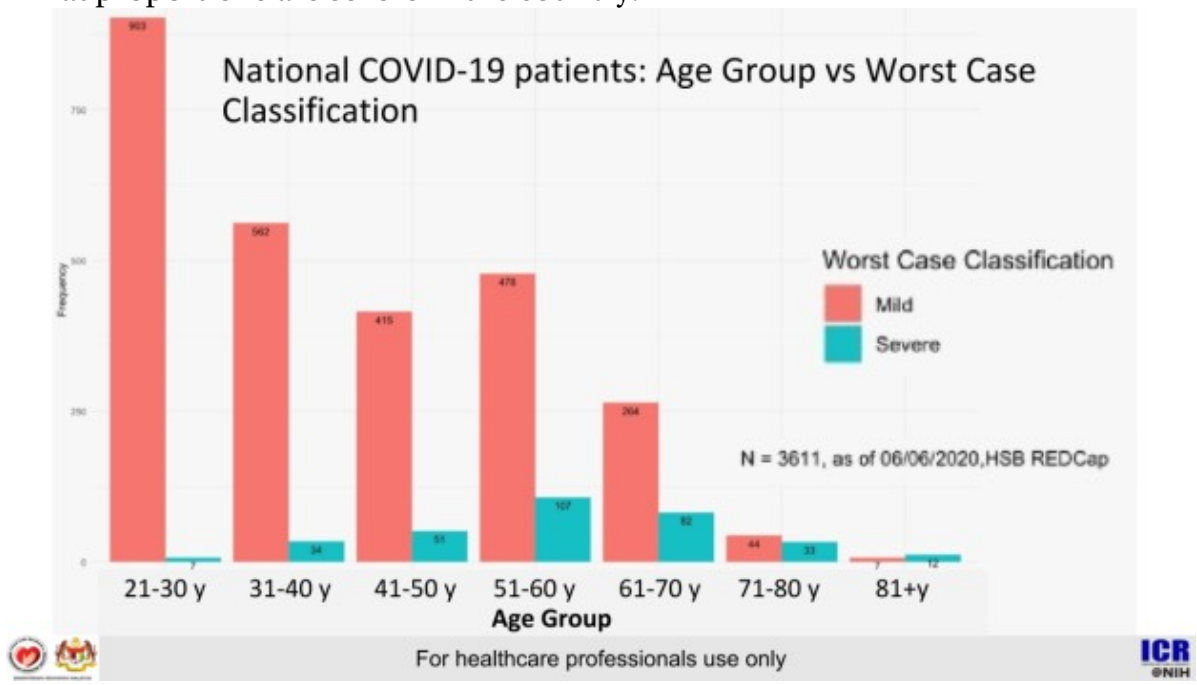


Diagram 2: Bar chart showing frequency of Malaysia's COVID-19 cases according to age group

Mild Disease-Clinical Category 1-3

What do we do with mild disease which means clinical category 1 and 2? In diagram 3, the bottom row is the day of illness. The mild COVID-19 patients have a viral response phase. Then, slowly the virus tapers off, and they get better. This virus response phase which can be associated with no symptoms, mild symptoms or pneumonia which does not require oxygen.

Diagram 3: Diagram showing viral response phase according to day of illness for mild COVID-19 disease

Severe Disease-Clinical Category 4 -5

When it comes to severe disease like category 4 and category 5, we would like to see *Who*, *When* and *How*.

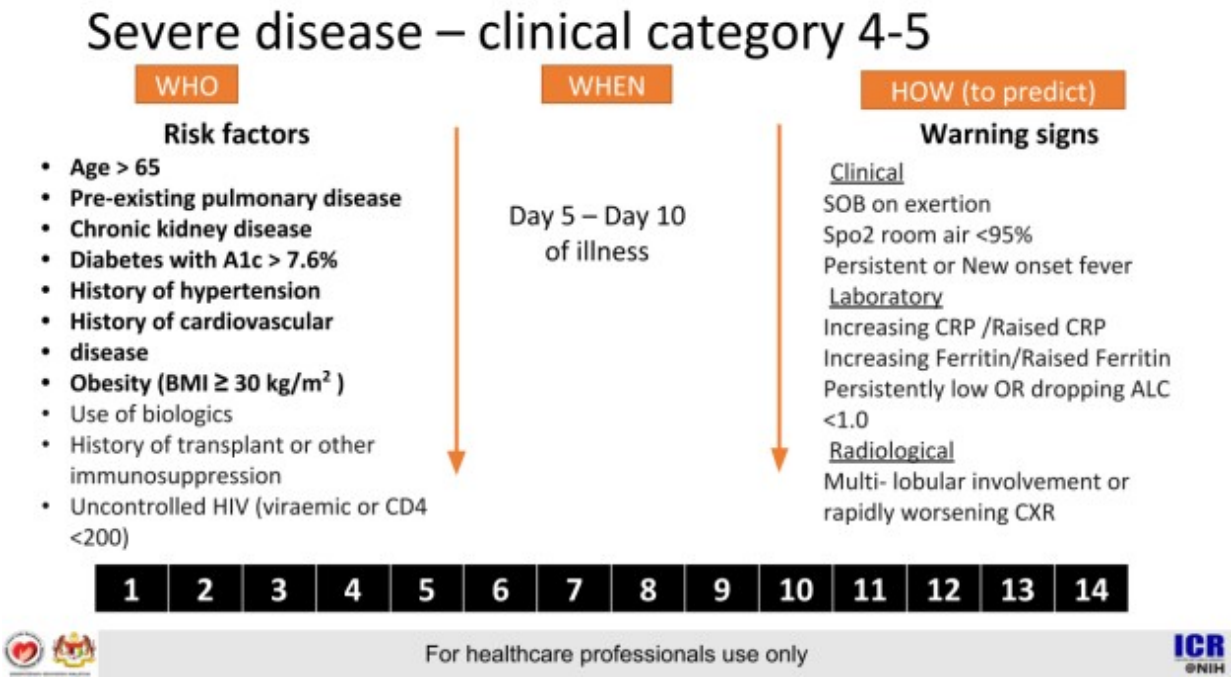


Diagram 4: How to detect those with severe COVID-19 illness?

Who gets this severe disease?

These are the risk factors for severe disease are the older age group, pre-existing pulmonary disease, chronic kidney disease, diabetes, which be HbA1c >7.6%, history of hypertension, history of cardiovascular disease and obesity. These are the ones who are more likely to get severe disease risk factors and these have been proven by literature.

When do people get severe disease?

We usually think they get it from Day 5 to Day 10 of illness. That's when severe disease usually happens.

What are the warning signs? What predicts that these people are going to get severe disease?

These are people who have shortness of breath on exertion, SpO_2 that is low, persistent or new onset of fever. These are the clinical features that tell us that this person is going to deteriorate.

Laboratory markers that indicate deterioration/warning sign will be:

i) increasing C-reactive protein (CRP)/raised CRP. We don't have solid data for it but our impression is CRP value more than 70-100 seems to be a warning sign,

ii) increasing ferritin/ raised ferritin to more than 500

iii) persistently low or dropping lymphocyte count <1.0, again is a warning sign. They might get severe COVID-19.

Radiological criteria will be a multi-lobular involvement or rapidly worsening chest x-rays. These are the features we look for. In all the cases, we look for risk factors, the duration of disease, how long they've been sick and the warning signs.

Severe COVID-19 Disease Group: Age

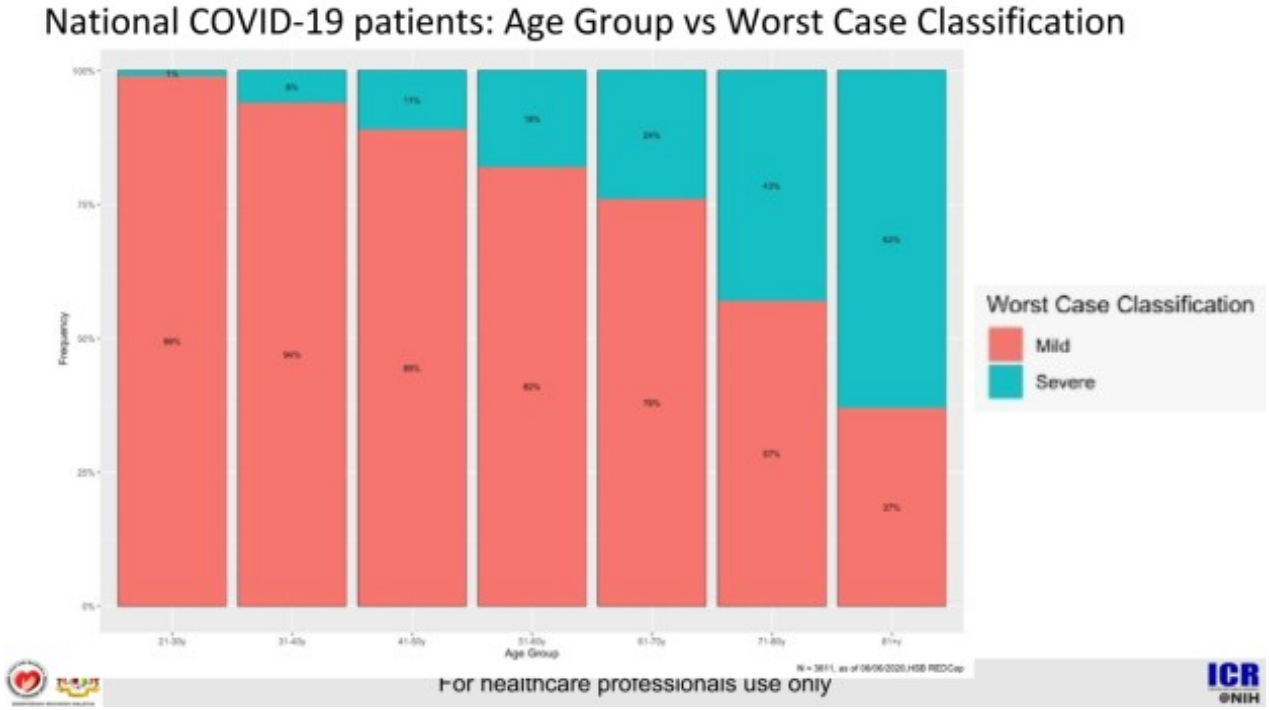


Diagram 5: Age is the most significant risk factor in COVID-19 disease

With regard to risk factors, the most significant risk factor is age. This is again data from our database looking at age group versus severity of COVID-19 disease. You can see that in the young age group, there is hardly anyone who gets severe disease. On the other hand, if you look at somebody who is more than 81 years of age, 63 % of them get severe disease. So, age by far is the most important risk factor for somebody to get severe disease.

Severe COVID-19 Disease Group: Cytokine Release Syndrome (CRS) Group

Moving on to the phenotypes of severe disease, as I have mentioned earlier that everybody has a viral response phase. People who get severe disease, especially one of the subgroups which I called now as a CRS subgroup where the host inflammatory response kicks in. It happens somewhere from Day 5 to Day 10 of the disease. The host inflammatory response kicks in, and they get severe disease. So, the severe disease is not because the virus is uncontrolled. The severe disease is because of the host inflammatory response.

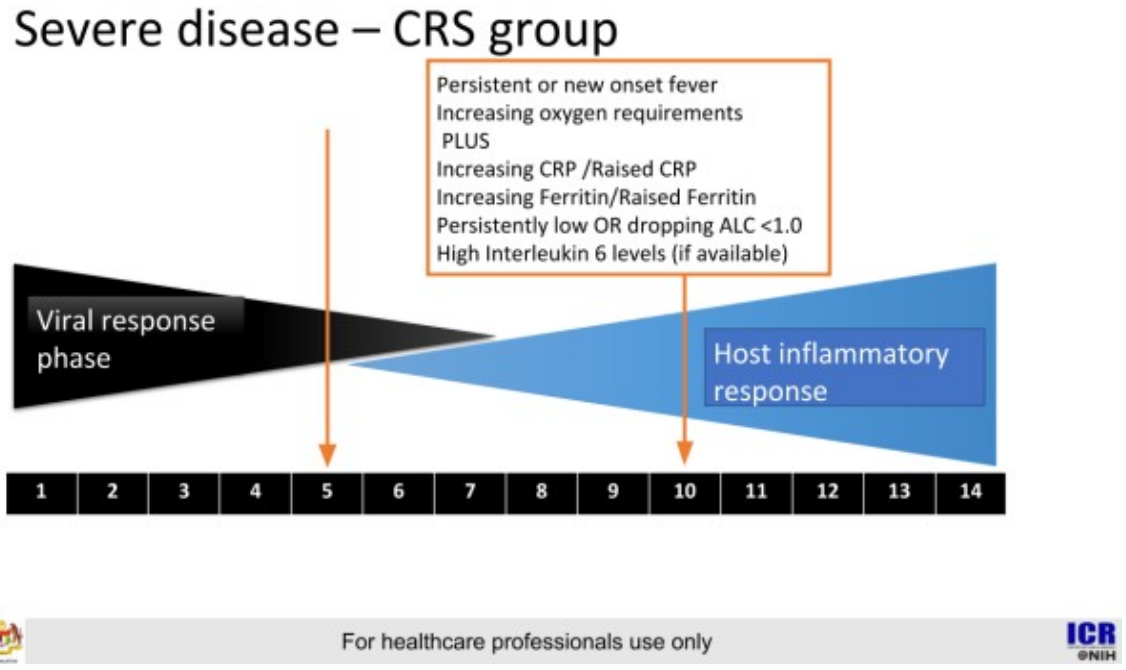


Diagram 6: Cytokine Release Syndrome

How do we pick up these patients clinically?

They are picked up by their persistent or new-onset fever, increasing oxygen requirement, increasing CRP, increasing ferritin and lowering or dropping absolute lymphocyte count and high interleukin 6 levels. So, when we have somebody who's becoming more hypoxic and along with it, we will see all these markers. It's sort of hints to us that this person is getting a severe disease because of host inflammatory response

Severe COVID-19 Disease Group: Comorbid Group

The second subgroup of patients that get severe disease is the ones that get comorbid. They have a viral response phase and then their comorbid medical condition worsens. So classically, we see that in end-stage renal failure patients who are dialysis dependent where they might require high-flow masks or even ventilation. But predominantly, it is because the comorbid medical condition is getting worse. There are some people who deteriorate purely because the co-morbid conditions are not in control.

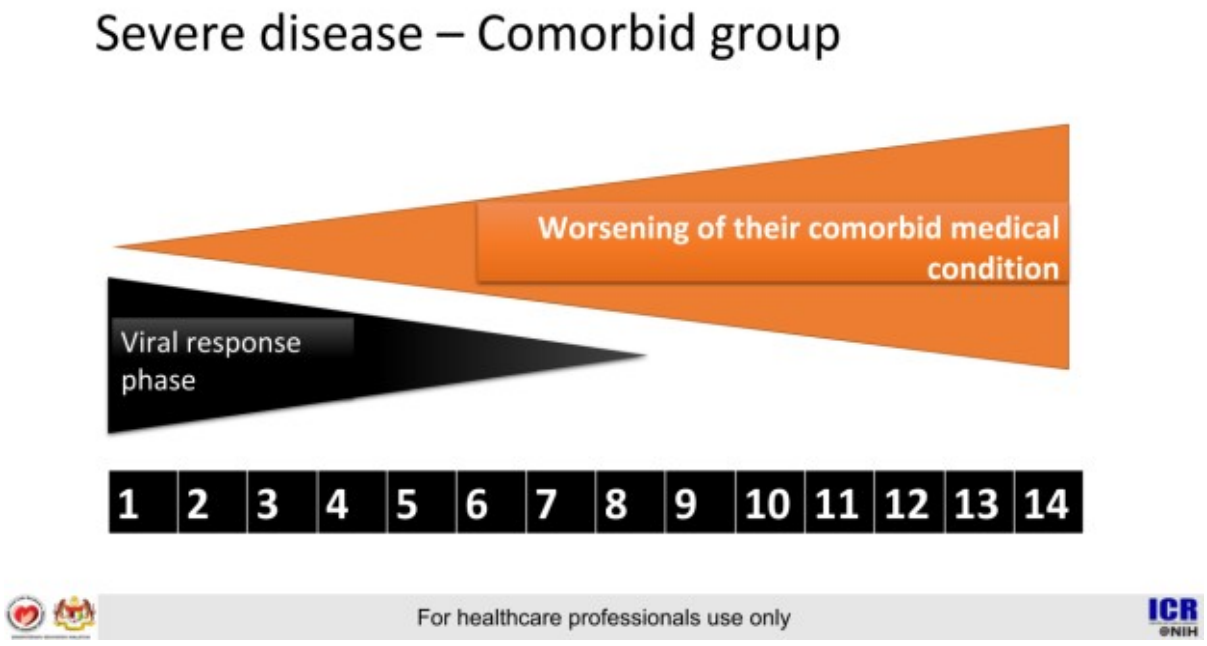


Diagram 7: Comorbid group as risk factor of severe COVID-19 disease

Severe COVID-19 Disease Group: Viral Pneumonia Group

The last group that gets severe disease is a viral pneumonia group, where their viral response is not in control at all. The host inflammatory response is there but it's not very prominent. This group of people have persistent new onset of fever and increasing oxygen requirements. However, all the markers about the inflammatory phase don't go up. So, this is a group where the viral response phase is predominant. Depending on the risk profile, the patients can be treated because of these parameters.

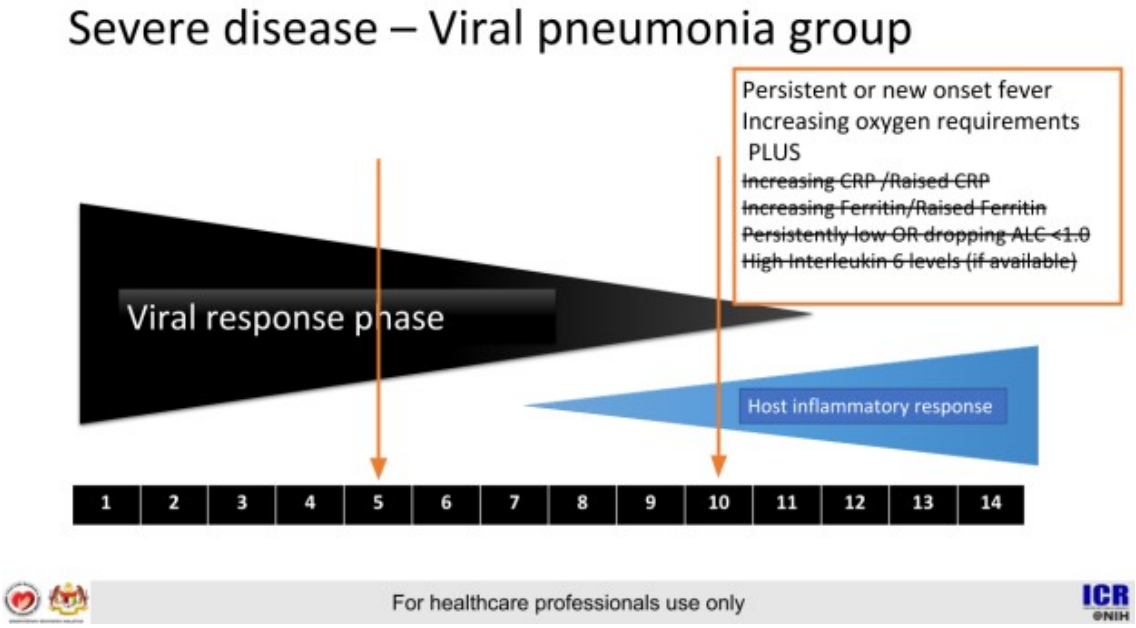


Diagram 8: Viral pneumonia group as the risk factor of severe COVID-19 disease

COVID-19 Treatment

When you looked at COVID-19 treatments, there are three modalities of treatment:

- Anti-inflammatory / immunomodulatory agents
- Antivirals
- Anti-coagulation

Anti - inflammatory / immunomodulatory agents

This is an early study conducted in Germany that looked at Interleukin 6 (IL-6) levels in 40 patients. One-third of them required ventilation [1]. If you look at IL-6 level, when IL-6 < 80 pg/ml, only 4% required intubation. When the IL-6>80 pg/ml, about 92% of them required intubation. The Il-6 started going up about 1.5 days before intubation. It sort of tells us that the IL-6 level predicted people who need intubation. So, there is an inflammatory response that needs to be tackled when we control COVID-19.

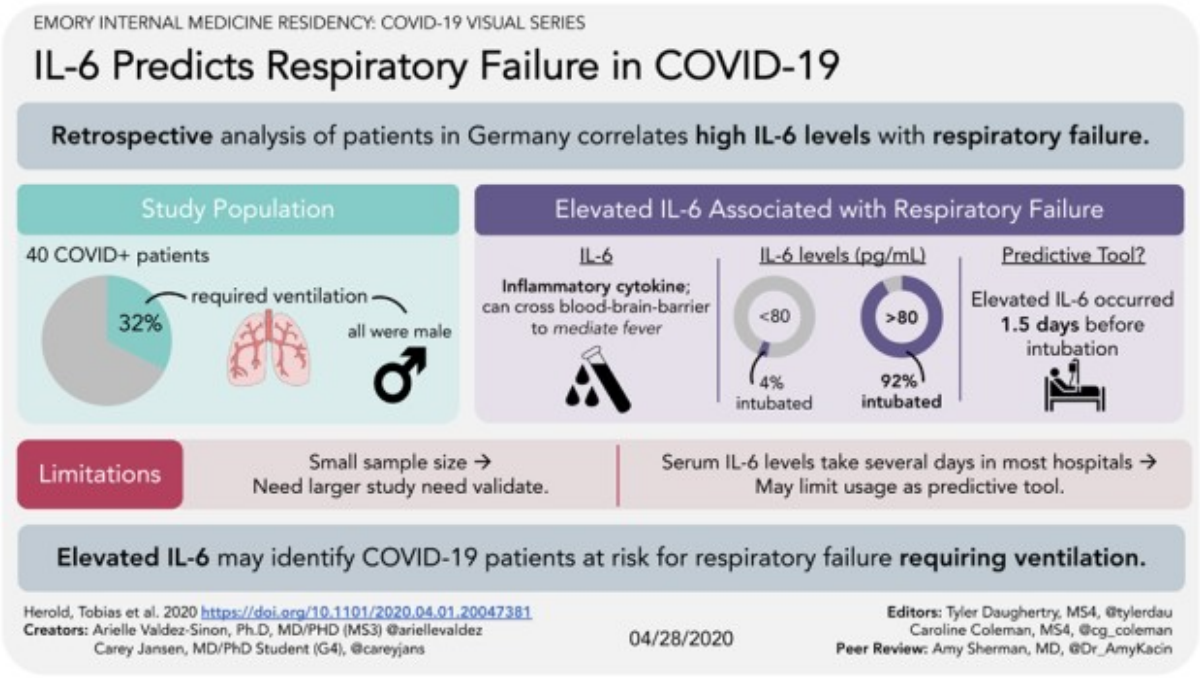


Diagram 9: COVID-19 patient with elevated IL-6 are at risk for respiratory failure may require ventilatory support (Image courtesy of Emory Internal Medicine Residency: COVID-19 visual series)

D-DIMER, CRP, Ferritin and Lymphocyte

There are subsequent studies. The study was done in Italy where an IL-6 inhibitor called Tocilizumab was given to patients with COVID-19 [2]. When Tocilizumab was given, the D-dimer rates were down, the CRP levels came down, the ferritin levels went down but a bit slower and absolute lymphocyte count went up. So, all these warning signs which I have spoken to you about, all have sort of recovered. The PaO_2 to FiO_2 ratio improved; the oxygenation improved. This shows that there is an inflammatory response especially the increased IL-6 and correcting it makes it better.

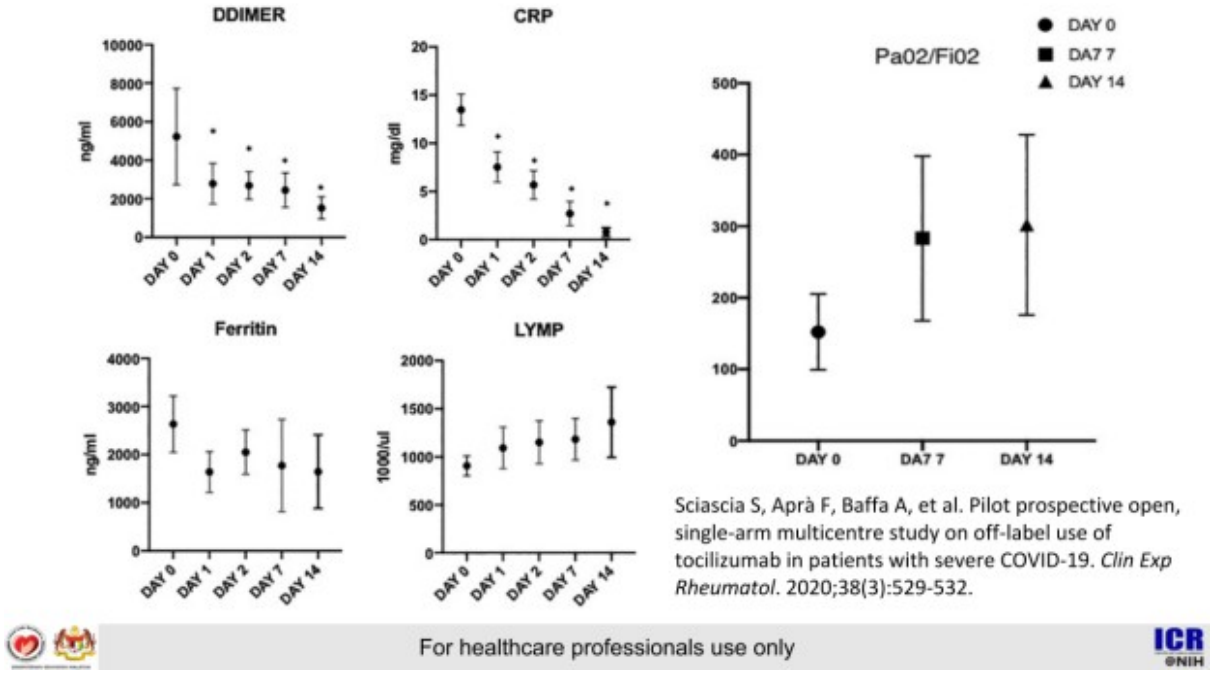
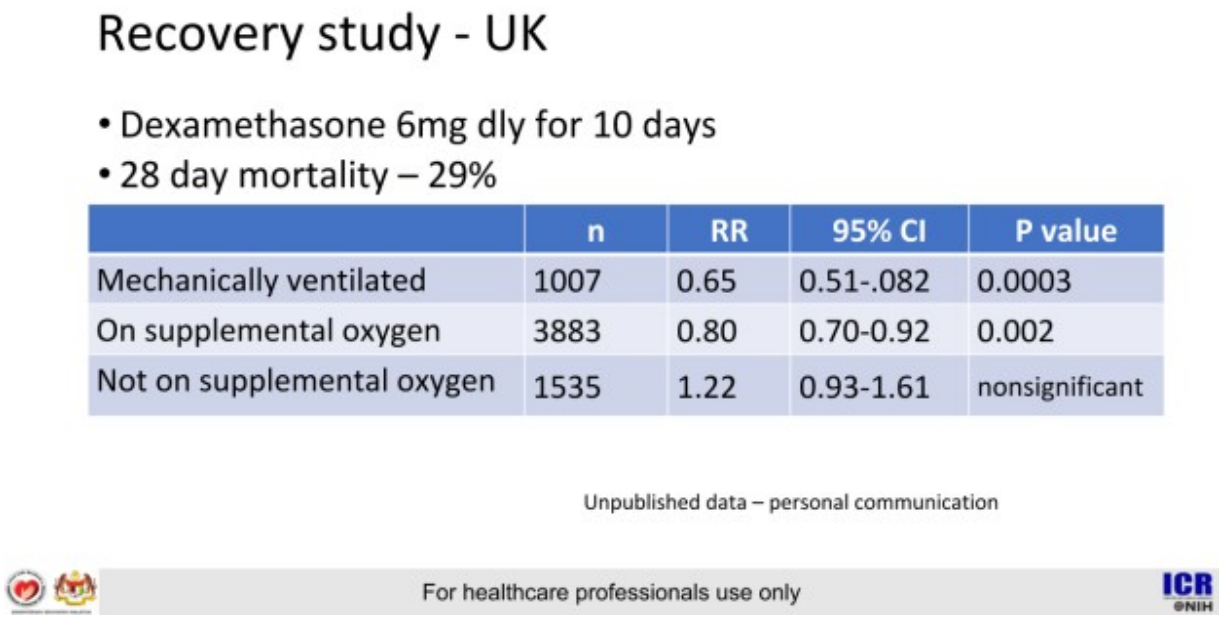


Diagram 10: Graphs showed laboratory parameters and respiratory parameters in a pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19

COVID-19 Recovery Study, UK - Dexamethasone proves first life-saving drug

In this particular study (through a press release, not yet published in journal), dexamethasone was given indiscreetly [3, 4]. Dexamethasone prescription was not based on the warning signs like CRP going up which I have spoken to you about. Everybody was given dexamethasone 6 mg daily for 10 days and then compared with the placebo group. They looked at 28-day mortality rates. The 1007 patients who were mechanically ventilated, dexamethasone improved the 28-day mortality by about 30% or 1/3. About 3883 patients who were on supplemental oxygen, dexamethasone improved the mortality by about 20 percent. But if the dexamethasone was given for people who were not on supplemental oxygen, there was no improvement in mortality. In fact, maybe you could argue there was some non-significant direction towards harm. This tells us that a big chunk of the deterioration in COVID-19 is because of inflammatory response. By giving dexamethasone to everybody, it actually decreases the mortality rate.



	n	RR	95% CI	P value
Mechanically ventilated	1007	0.65	0.51-.082	0.0003
On supplemental oxygen	3883	0.80	0.70-0.92	0.002
Not on supplemental oxygen	1535	1.22	0.93-1.61	nonsignificant

Diagram 11: Unpublished findings from Recovery Study, UK [3, 4]

MOH guidelines

Patients in category 4 and 5 are those who require oxygen, we need to look out for markers suggestive of cytokine release syndrome (CRS). If any of these criteria (below) is present, then our recommendation is to give dexamethasone, methylprednisolone or tocilizumab.

Clinical:

- *Persistent or new onset fever*
- *Increasing oxygen requirement*

PLUS

- *Increasing CRP /Raised CRP*
- *Increasing Ferritin/Raised Ferritin*
- *Persistently low OR dropping ALC <1.0*
- *High Interleukin 6 levels (if available)*

We are giving a shorter course of dexamethasone as compared to what is recommended in the Recovery study. This is our own recommendation:

IV Dexamethasone 4mg bd or tds - 3- 5 days
OR
IV Methylprednisolone 1-2mg/kg daily - 3- 5 days
OR
IV Tocilizumab 4-8mg/kg single dose - preferred in late presentation

We are still continuing with this particular recommendation which means we are not giving it to everybody that requires oxygen. We are looking for markers of high cytokine release before giving it. That's regarding anti-inflammatory/ immunomodulatory agents

COVID-19 Treatment - Antiviral

Treatment Likely To Be Effective Only If Given Early

Early on, there was a randomized study done by the Chinese group that looked at Kaletra (lopinavir-ritonavir), a HIV drug repurposed to treat COVID-19 [5]. The final result of the study showed that lopinavir-ritonavir did not make a difference. However, some information came out from that study that we need to give antivirals early. The first graph showed that there is no lopinavir-ritonavir given for less than 10 days of illness. When lopinavir-ritonavir was given for less than 10 days of illness, it makes a difference with regard to the number of people who become COVID-19 negative. Overall, the final results showed no difference but it looks like for antiviral to work, it needs to be given early.

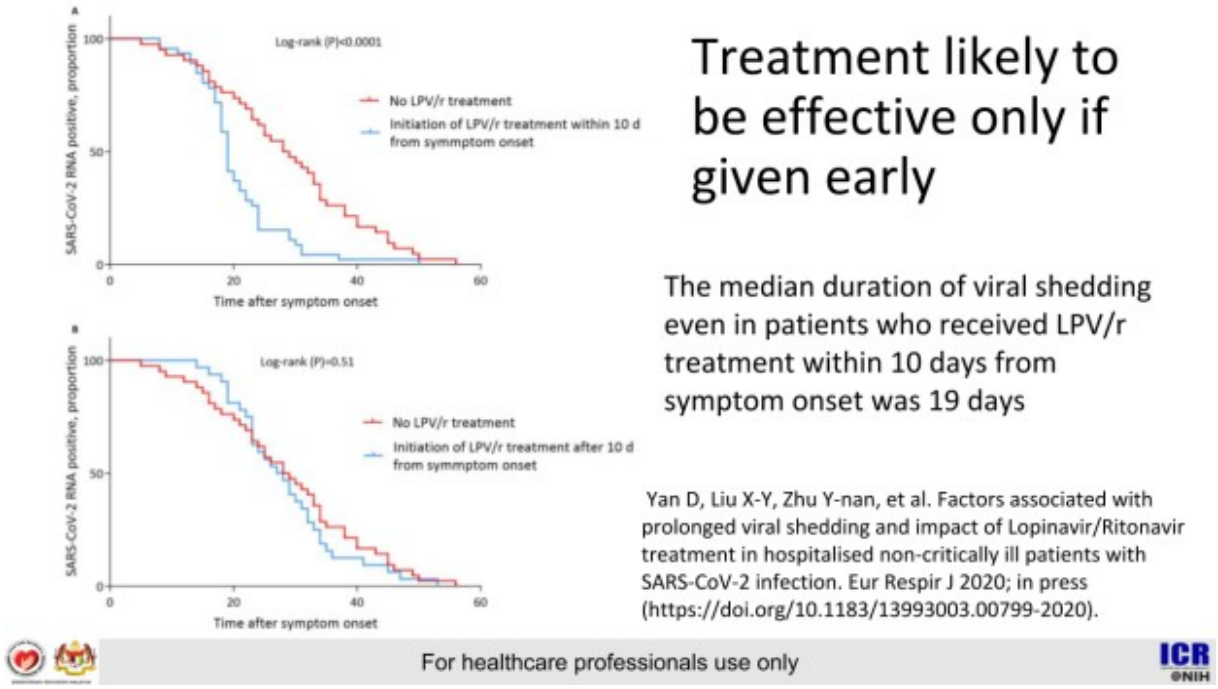
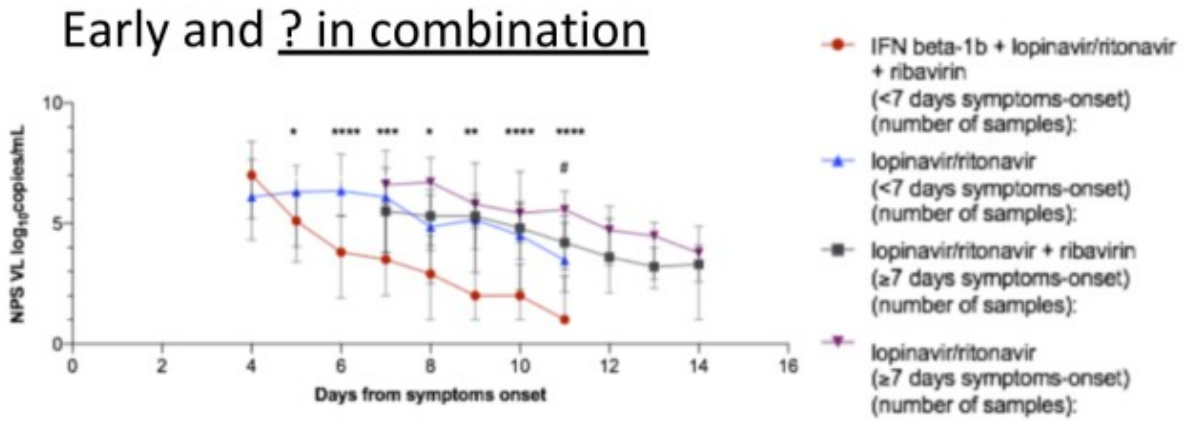


Diagram 12: Findings from the study on impact of lopinavir-ritonavir on COVID-19 patients by Yan et al.

Early and Antiviral combination

This is a study from Hong Kong. They tried with 3 drugs: interferon beta, lopinavir-ritonavir and ribavirin [6].

The result showed that using the three drugs at <7 days symptoms-onset has the best outcome. The worst outcome was when lopinavir-ritonavir alone was given at ≥7 days symptom-onset. So, it looks like if you were to use antivirals as a treatment modality, maybe we need in combination and also have to be given early. So, this particular study shows that we probably need to give it at < 7 days of disease.



Hung, I.F.-N., Lung, K.-C., Tso, E.Y.-K., Liu, R., Chung, T.W.-H., Chu, M.-Y., Ng, Y.-Y., Lo, J., Chan, J., Tam, A.R., et al. (2020). Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet.

Diagram 13: Hung et al. study showed that combination antiviral therapy and early treatment has better outcome than single antiviral

Remdesivir for the treatment of COVID-19: baseline characteristics

The most recent studies looked at Remdesivir for treatment of COVID-19 done in the US [7]. These are the baseline characteristics of patients in diagram 15. Majority of the patients were given Remdesivir. It is for

- hospitalized patients who were receiving supplemental oxygen,
- hospitalized patients who were not in supplemental oxygen,
- hospitalized patients who were not on invasive ventilation and
- hospitalized patients who were on invasive mechanical ventilation.

These are the 4 groups of patients, and they had about 1000 patients: 541 patients on Remdesivir and 522 patients on placebo.

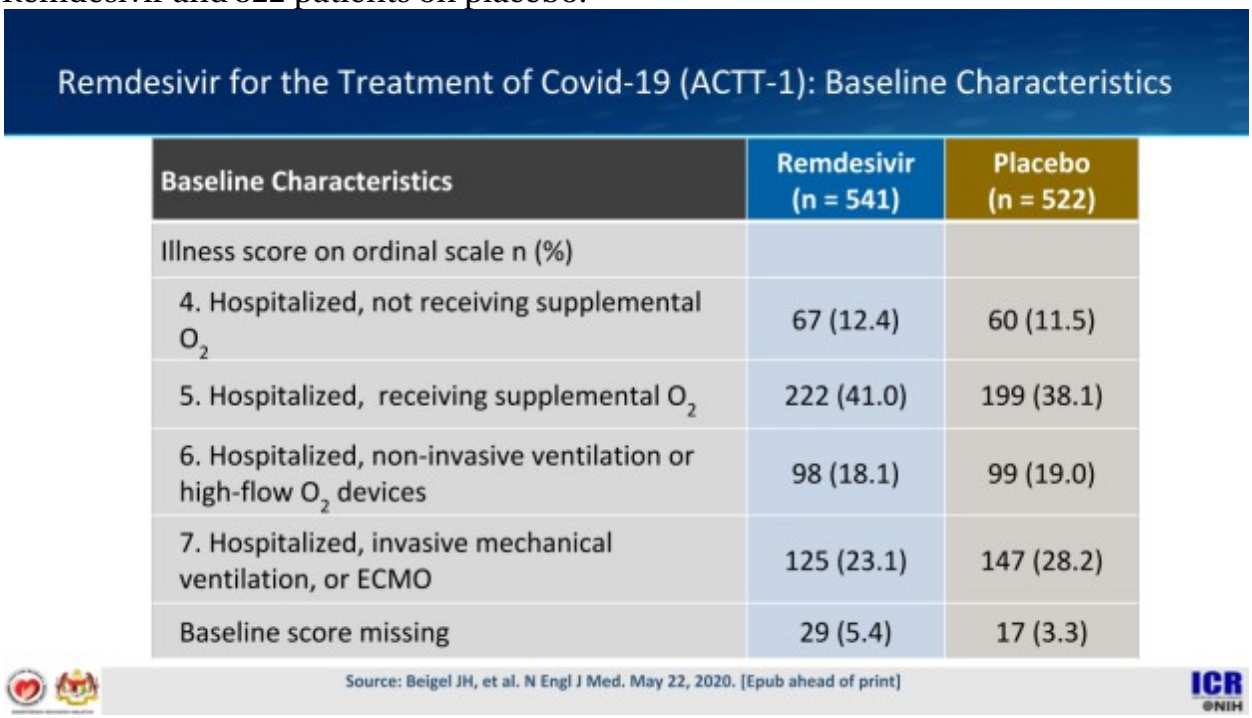


Diagram 14: Baseline characteristics in the Remdesivir for the treatment of COVID-19 by Beigel et al.

Remdesivir for the treatment of COVID-19: results, days to recovery

The data showed that the ones (mild - moderate category) that did not require oxygen, the outcome was no different between the Remdesivir and placebo groups [7]. They were looking at the days to recovery, meaning how many days it took to go back to category 1 and 2. At least 2 categories had pointed to less days to recover because the study was published so fast that they couldn't look at mortality data yet. The overall study showed that the patients who took Remdesivir became well faster, at day 11 while patients who took placebo became well slower. It took 15 days. Most of the data was in the severe groups where it took 12 days to recover for the Remdesivir group and 18 days in the placebo group. There was no difference in the two groups that did not require oxygen (mild - moderate disease groups). So, the question is whether the milder group ever needs to give them antivirals or not?

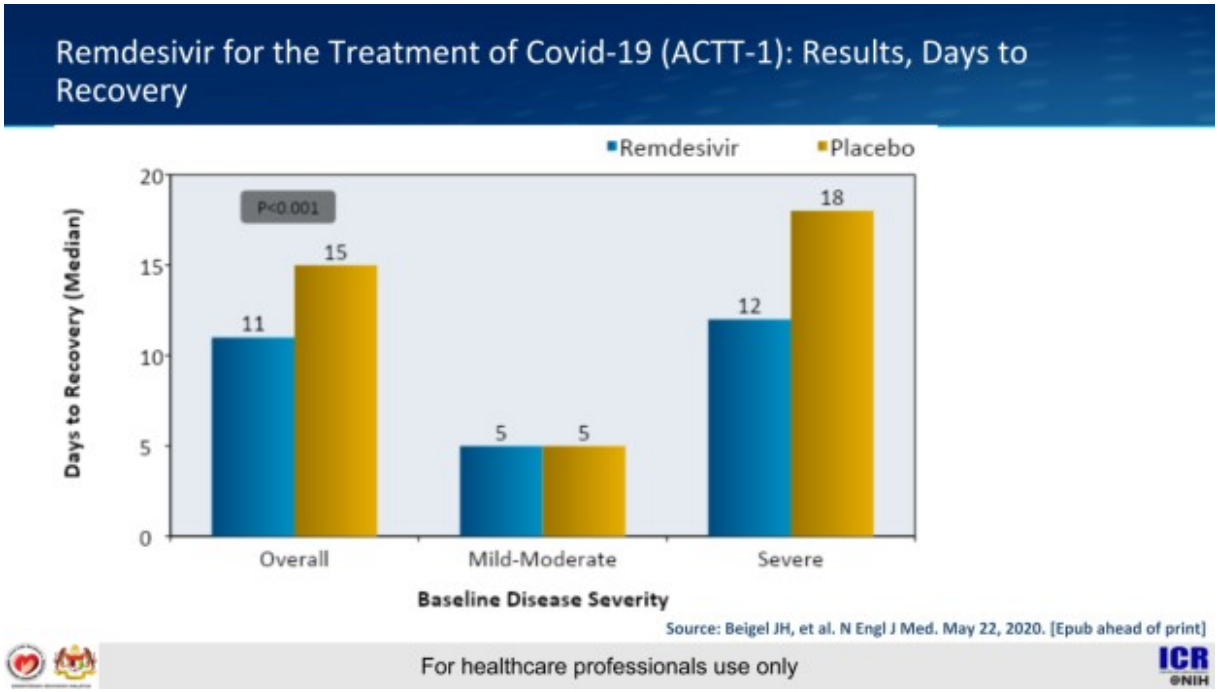


Diagram 15: Comparison of Remdesivir and placebo treatment arm in terms of days to recovery and severity of COVID-19 disease.

Remdesivir for Treatment of COVID-19: Mortality Results

They did not have complete data for mortality because it was published very early. The overall mortality benefit was 0.70 or 30% of the better mortality rate, but it was not a significant difference [7]. Overall, there was no mortality benefit. The study was either not powered enough for that or the study was terminated too early. The best signal was for category 5, in patients who require oxygen. In category 6 and category 7 where the patients required ventilation and or acquired high-flow masks and non-invasive ventilation, it did not seem to make a difference. Maybe the antiviral alone is not enough in these groups. Maybe what the UK recovery study did was the anti-inflammatory drugs were required in these particular groups. The antivirals made a difference in these groups as far as mortality benefit is concerned. But none of the data were statistically significant. We are waiting for more data from this particular study.

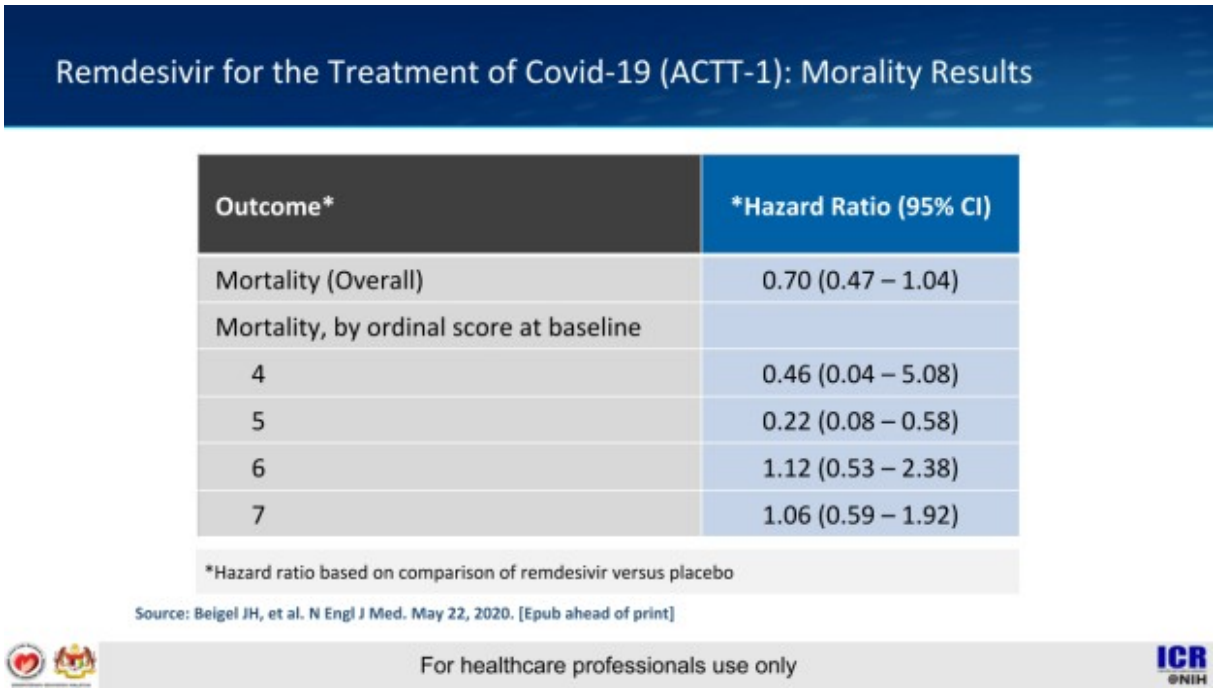


Diagram 16: Mortality data from the Remdesivir for the treatment of COVID-19 study by Beigel et al.

Treatment with Favipiravir

Favipiravir is available in Malaysia currently, but not available in many of the Western countries. This was a before and after study comparing Favipiravir with lopinavir-ritonavir [8]. They looked at the positive rate. It showed that favipiravir compared to Kaletra was a better antiviral as far as bringing down/making the nasopharyngeal swabs negative is concerned. It brought it down faster.

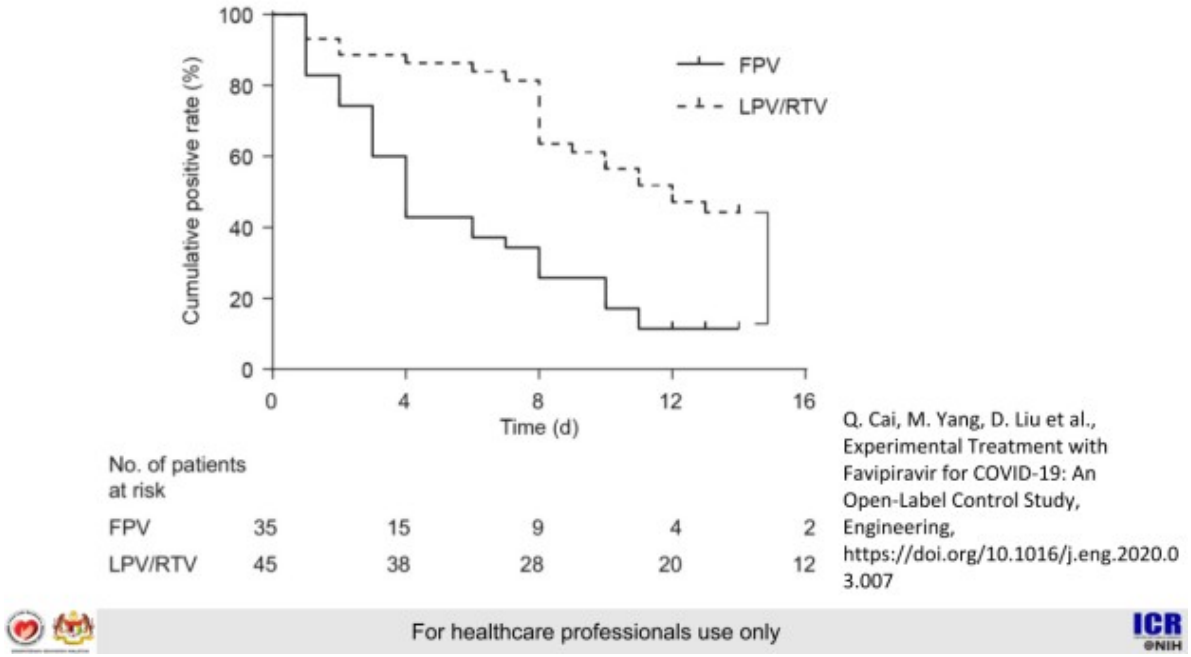


Diagram 17: Study by Cai et al. comparing Favipiravir and Kaletra in an open-label control study

This was translated into better chest CT scan results. The CT scan improvement also was higher in the favipiravir group compared to the kaletra group. The patients in the study arm were mild cases and none of them had passed away or on ventilators. That was why we were not able to look at the mortality rates.

Chest CT changes in patients with COVID-19 after treatment.

Chest CT changes	COVID-19 patients (N = 80)		
	FPV (N = 35)	LPV/RTV (N = 45)	P value
Day 4 after treatment			
Improve	8 (22.86%)	8 (17.78%)	
Worse	9 (25.71%)	15 (33.33%)	
Constant	18 (51.43%)	22 (48.89%)	0.42
Day 9 after treatment[a]			
Improve	18 (56.25%)	16 (35.55%)	
Worse	8 (25.00%)	16 (35.55%)	
Constant	6 (18.75%)	13 (28.90%)	0.11
Day 14 after treatment			
Improve	32 (91.43%)	28 (62.22%)	
Worse	1 (3.23%)	9 (20.00%)	
Constant	2 (6.45%)	8 (17.78%)	0.004

[a] For three patients in the FPV arm, the lung CT scan on Days 6–9 after medication was not carried out.

Q. Cai, M. Yang, D. Liu et al., Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Engineering, https://doi.org/10.1016/j.eng.2020.03.007

Diagram 18: Chest CT changes in patients with COVID-19 after Favipiravir and Kaletra treatment in an open-label control study

Retrospective Analysis of Hydroxychloroquine in 84 Hospitalized Patients With COVID-19: Study Arm

There are many studies on hydroxychloroquine. I just want to put up one study, the French study that said that "hydroxychloroquine is a wonder drug and nobody should live without the drug". It is actually a retrospective cohort study where they looked at all their patients who were on hydroxychloroquine versus those who are not on hydroxychloroquine [9]. They tried to balance all the relevant confounding factors like age, gender, comorbidities, BMI>30kg/m^2, 3rd trimester of pregnancy, treatment with angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), times since symptom onset and severity of disease. These are all the important parameters which they have adjusted for.

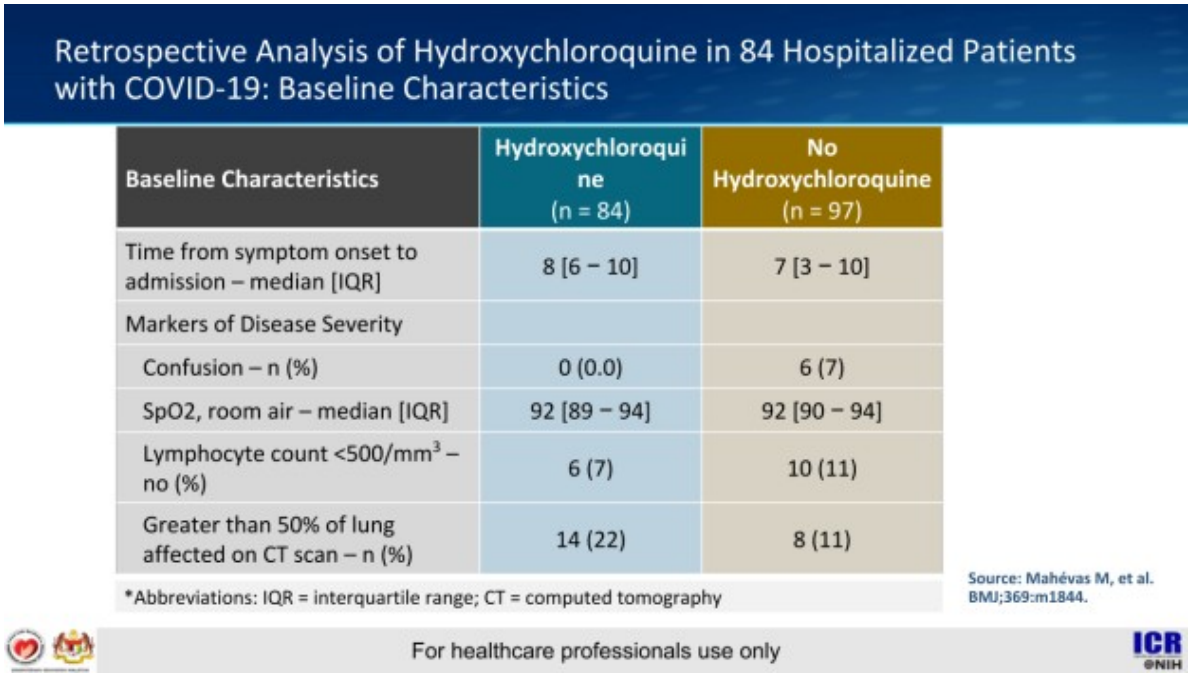


Diagram 19: Baseline characteristics of patients in the hydroxychloroquine study by Mahévas et al.

Hydroxychloroquine was given to patients who were around Day 8 of illness. Many of them actually require oxygen, SpO2 of 92%.

They found that there were no significant differences between the groups in relative risk of:
i) transfer to ICU or death within 7 days,
ii) all causes of mortality within 7 days and
iii) development of ARDS.

Of the 84 patients who received hydroxychloroquine at admission, 8 (9.5%) developed an electrocardiogram (ECG) change requiring discontinuation of hydroxychloroquine (7 experienced QT prolongation and 1 developed 1st degree AV block). 1 of the 8 patients in the no initial hydroxychloroquine group who subsequently received hydroxychloroquine developed a left bundle branch block.

Malaysia's HCQ – Before and After Study

Our data with 586 patients in stage 2 and stage 3. We were looking at patients with mild disease to start hydroxychloroquine. These patients did not require oxygen. 451 were initiated on hydroxychloroquine regimen for at least 5 days. We compared them with 135 historical controls without hydroxychloroquine.

This is because at that particular juncture, before national guidelines on hydroxychloroquine were implemented, we were using only Kaletra for the 135 cases, especially in Hospital Sungai Buloh and Hospital Permai in Johor Bahru.

We were hoping that the hydroxychloroquine arm would have prevented deterioration. Our data showed the proportion of deterioration to the stage 4 and 5 was 10% for hydroxychloroquine and without hydroxychloroquine was 8.9%. They were not statistically significant. Hydroxychloroquine doesn't seem to prevent deterioration to rapid disease.

We also adjusted for confounding factors to see if there was any difference in results. Based on this data and the data from WHO Solidarity Study that's going to come out, hydroxychloroquine is not going to make a difference. I think the hydroxychloroquine era or in Malaysia may stop, and we will not be using hydroxychloroquine for COVID-19 for the time being.

NIH Study

The definitive data coming out from this NIH study involving 2000 patients [10]. They are looking at people who were diagnosed with early COVID-19 disease (symptoms within 24 hours of screening). Those who were hospitalized were excluded from the study. They want to see whether hydroxychloroquine started at very early will prevent hospitalization. This will be the conclusive study about hydroxychloroquine.

MOH Guidelines

Based on the MOH guidelines, for category 4 and 5, we use:

Lopinavir-Ritonavir 2tabs BD OR Atazanavir 300mg daily and Ritonavir 100mg daily AND

Favipiravir 1600mg BD for 1 day then 600mg BD (teratogenic).

If < 7 days of illness:

- *SC interferons Beta 1a 44mcgm stat then EOD OR*
- *Interferon Beta 1b 250mcg stat then EOD (3-5 doses)*

We have to remember that favipiravir is teratogenic, and we have to be careful in the reproductive age group.

If <7 days of illness, data from Hong Kong showed that they were using interferon beta therapy and if > 7 days, they use these two drugs. These are the drugs which are part of our registry. We will analyze the data the same way as we have analyzed the data with hydroxychloroquine from time to time and revise our guidelines.

We still don't know whether category 3 with risk factors or category 3 with warning signs; should we start treatment? Category 4 and 5 are clear in terms of treatment.

COVID-19 Treatment - Anticoagulation

Addressing Hypercoagulopathy

There is a large amount of literature out there now stating that COVID-19 causes hypercoagulability. We had four to five patients who had confirmed pulmonary embolism due to COVID-19. We divided how we should address hypercoagulability into 3 treatment groups:

- Full dose anticoagulation
- Prophylaxis
- High prophylactic dose anticoagulation

The first two groups are quite clear. The current data says we need to do a **full dose of anticoagulation**. For example, if enoxaparin is used, we have to use 1 mg/kg 12 hourly for patients with normal renal function. A full dose of anticoagulant should be started if

- anybody with confirmed venous thromboembolism,

- anybody with suspected pulmonary embolism i.e. they have sudden deterioration in oxygenation or hemodynamic instability, acute cor pulmonale or

- anybody with clotting of vascular devices (eg, venous, arterial devices, and hemodialysis devices).

I was told by my intensivist, Dr Lee CK that the Continuous Renal Replacement Therapy (CRRT) is more often clotted in COVID-19 patients, more than other critically ill patients. So all these patients should get their full dose of enoxaparin.

For **prophylaxis**, 30 to 40 milligrams enoxaparin daily depending on renal function will be given. We give it to all patients who require supplemental oxygen. For anybody

in category 4, we started them on anticoagulant prophylaxis. However, the current literature or data from Europe showed that a lot of these patients while on prophylaxis are still getting venous thromboembolism. There is a recommendation to use high prophylactic dose anticoagulants for these patients.

What is called a high **prophylactic dose anticoagulant**? Meaning the dose is something like enoxaparin 0.5 mg/kg 12 hourly. It is still controversial as different centres recommend different things. Some recommended high prophylactic dose anticoagulants for all ICU patients and some said we should base on the increased D-dimers values. Again, the D-dimers cut off values are different. Some use the value of 3000 as cut-off and some use the value of 5000 as cut–off point. We will discuss this and come up with a consensus.

Other Interventions

What made a difference is not only the treatment: antiviral, steroid or anticoagulant treatment. It is also other interventions like the monitoring guidelines, self-proning & CRIB or drug interaction which makes a difference.

Monitoring Guidelines

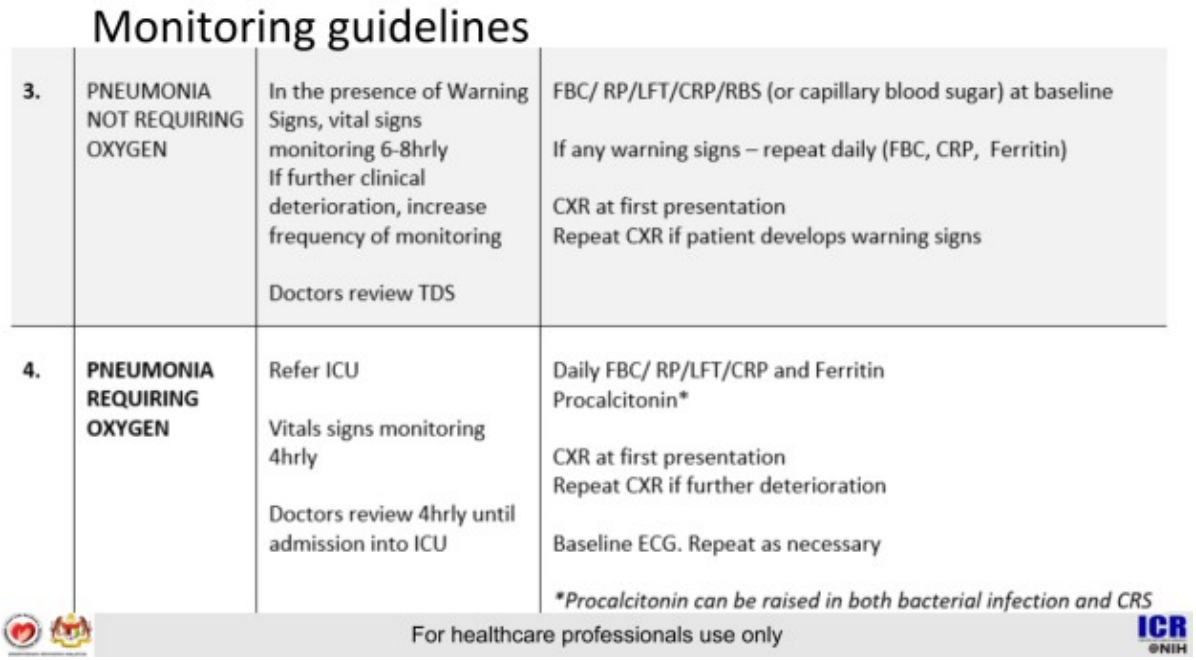


Diagram 20: Monitoring guidelines by MOH, Malaysia

Based on the way we managed dengue, we came up with clear guidelines on how often to take laboratory tests to monitor for warning signs or pick up those warning signs. If somebody is in Category 3, we have to review the patient's three times to look for these warning signs as well as any clinical deterioration.

If somebody requires oxygen as in category 4, we have to monitor them 4 hourly. We have to do all these blood tests to look out for the cytokine release syndrome, so that we can start anti-inflammatory/ immunomodulatory therapy early.

Self Proning, CRIB and Drug Interaction

We are also learning from the Chinese group. The patients who are having exertional dyspnoea are encouraged to do self-proning. We also asked them to have complete rest in bed (CRIB) as far as possible.

For every single drug that we use, we go to this particular website:https://www.covid19-druginteractions.org/ to look for drug interactions. This is because many of the drugs that we use have a lot of drug interaction especially in ICU as they can all prolong the QT interval.

That's it. Thank you.

Slide link: https://cutt.ly/DuRDqNu

Webinar: https://youtu.be/qmrTGkM4EOE

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“COVID-19 Mortality Review in Malaysia” by Dr. Faizah Muhamad Zin, Medical Development Division, MOH

**This is a preliminary finding of COVID-19 mortality review in Malaysia. A manuscript paper will be published soon by the Ministry of Health, Malaysia. So, no slide is available after the webinar.*

Introduction

A very good afternoon everyone. I am Dr. Faizah from the Medical Development Division. My presentation today is on COVID-19 mortality review. We are the members of the National COVID-19 Mortality Review Committee. The committee was established in March 2020.

Outlines

As the outline of my presentation, I am going to start with the background of the committee. Then we will go through the overview, the demographic and clinical profile data of our mortality review, the risk factors, a little bit on the clinical management data, our findings, recommendations and some directives that had been circulated from our Deputy DG & Director General (DG) of Health offices.

Background

On the 20th March, during the National Crisis Preparedness and Response Centre (CPRC) meeting which was chaired by our DG of Health, he had decided to form a National COVID-19 Mortality Review Committee. As you know, the first COVID-19 death was reported on the 17th of March 2020. Subsequently, the decision to form a committee was decided during the CPRC meeting.

On the 23rd March 2020, we had our first discussion with the chairman, Datuk Dr. Christopher Lee. The objectives of the committee were to review the COVID-19 mortality cases, to look at the systemic issues and to identify the areas for improvement in order to make recommendations based on the review, in the pursuit of improving patient outcomes and to reduce morbidity & mortality among the COVID-19 patients. From the 27th March until the 18th of June 2020, we had intensive review of the cases. In total, we had 13 meetings. We were a bit aggressive during the initial phase because the death kept on increasing during the initial phase of COVID-19 pandemic. We had weekly meetings on every Tuesday and Friday. The first two initial meetings were physical meetings and subsequently followed by teleconferencing meetings.

How do we do it?

We collected all the patients' records from the respective hospitals and we discussed each case in detail during the mortality review meeting. Bear in mind, we have to look at every page on the patients' clinical case notes. We got the committee members to review and present the cases and the committee comments on the management course of the case. Subsequently, based on the discussion, the committee came out with the recommendations based on the cases.

The Committee

The committee is chaired by Datuk Dr.Christopher Lee. The members of the committee are esteemed medical consultants from various fields include Dr.Melor, Dr.Letchumanan, Dr.Shanti Rudra Deva, Dr.Asri, Dr.Anusha, Dr.Siti Suhaila, Datuk Dr.Kauthaman, Dr.Hidayah, Dr.Khairil, Dr.Azaini, Dr.Siew, Dr.Fazilah, Dr.Nor' Aishah and Dr.Shahanizan. I am one of the members and Secretariat together with my team, the Clinical Audit Unit.

Definition of COVID-19 death

In January 2020, the World Health Organization (WHO) defined the COVID-19 death as the death of a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms. We followed this definition when we had our first COVID-19 mortality case on March 17th, 2020.

The definition of COVID-19 mortality rate is the number of deaths with positive COVID-19 laboratory tests divided by the number of positive cases at the given period of time.

However, after we had followed the initial definition, on the 16th April 2020, WHO had published the "International Guidelines for Certification and Classification (Coding) of COVID-19 as Cause of Death". It was stated that:

> *"a death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19."*

The countries who had their first death after the 16th April 2020, they would use this new revised definition, but for us, we are still using the initial WHO's definition.

Overview on mortality rates in the region

This is a comparison between ASEAN countries. The mortality rate for Malaysia to date until yesterday (17th June 2020 at 12 PM MY Time) was 1.42% as compared to Singapore which was 0.06%, Thailand 1.85%, Myanmar 2.29% and Philippines 4.07%. In Indonesia, the mortality rate was 5.49%.

Malaysia-COVID-19 Death

The graph showed the summary of our mortality cases from 17th March 2020 until yesterday (17th June 2020 at 12 PM MY Time). The first mortality case was on 17th March 2020, and we have reached the highest number of COVID-19 mortality cases (n=6 in a day) around the end of March 2020 until mid of April 2020 (n=6 in a day). Our first recommendation from the COVID-19 Mortality Committee came out on the 30th March 2020. Subsequently, we had a series of recommendations. After we reached our peak around mid-April 2020, we started to have a slope down on the graph. Our number of deaths tapering down to more or less zero to one per day until yesterday. At this point of time, our death numbers were 121 and the number of positive cases in Malaysia were 8515.

Mortality Rate (by State)

Based on the mortality rate by states, the state with the highest mortality rate is Perlis followed by Sarawak, Johor and Perak. Kuala Lumpur, the federal territory has high mortality rates because KL has a few big hospitals like Hospital Kuala Lumpur (HKL), UM Medical Centre, National Heart Institute (IJN) and UKM Medical Centre. Perlis is a small state and the high mortality rate is because of the small number of positive COVID-19 cases (small denominator).

Number of Mortality (by Hospital)

Again, we do not assume that Hospital Kuala Lumpur (HKL) is not doing well. In Malaysia, as part of our preparedness in facing the pandemic, we have classified our hospitals into COVID-19 hospitals, hybrid hospitals and non-COVID-19 hospitals. HKL happened to be a hybrid hospital where Hospital Kuching, Hospital Kluang and Hospital Sungai Buloh are COVID-19 hospitals. When we have classified it that way, it is natural to see that the number of deaths would be higher in these hospitals compared to other hospitals.

Cause of Death

Based on the death certificates, about 81% of the cause of death was contributed by pneumonia. When pneumonia set in, they started to have multi-organ failure and Acute Respiratory Distress Syndrome (ARDS). Having said that, there were a few incidences, around 10% of the patients died due to acute coronary syndrome (ACS). Perhaps this was due to the complications of the disease itself or due to the primary disease. Most of the patients have multiple comorbid conditions such as hypertension, Diabetes Mellitus and obesity. Some of them were well known cases of heart diseases or coronary artery diseases. There were about 4% who died due to malignancy, and a few isolated cases whereby the cause of death was due to acute pulmonary oedema, hanging, severe dehydration, ruptured abdominal aortic aneurysm (AAA) and one was unknown cause. The unknown was due to the fact that we do not have any information of the deceased.

Demographic & Clinical Profile

Number of Deaths According to Nationality

The majority of our deaths were Malaysian, 96%. The non-Malaysian contributed to about 3.3% and unknown, 0.8%

Gender-Specific Mortality Rate

As we know, male mortality is higher than female in terms of the mortality number (72.7%) and the number of positive cases. Male and female mortality rates, however, were about the same in Malaysia, whereby male is about 1.43 % and female is 1.41%.

Age-Specific Mortality Rate

Our findings are the same like other countries in the world. The older you are, the more severe the disease you will get. Based on our data, those who were below 50 years old, mortality rate is less than 1%. For those who were aged 50 to 59 years old, the mortality rate is 1.87% and aged 60 to 69 years old, the mortality rate is 5.28%. If you look at those above 80 years old, the mortality rate contributed to about 22% of our data and aged 70 to 79 years old contributed to about 12% of the mortality.

Duration of the Onset of Symptoms until Death

When we look at the duration of the onset of symptoms until death, the mean is about 16 days. Majority of them died after the onset of symptoms of more than 9 days. It is about 87%.

Duration of the Onset of Symptoms to Admission

If we look at onset of symptoms to admission, the majority of patients presented to us on average is about 7 days. Majority of them came after a week, meaning, it is a late presentation. Based on clinical articles, the best time to catch them is during the onset of symptoms of less than 5 days. In our data, most of them came after 7 days.

Time of Admission until Death

Most of the patients managed to survive more than 9 days. About 50% of them stayed in our hospital for more than 9 days. The mean is around 10 days.

Stage of Disease at Presentation (at admission)

The stage of disease presentation here referred to Malaysia's COVID-19 disease severity classification. Majority of our cases came late. About 21.4% came at Stage 3; 57.1% came in at Stage 4; and 14.3% came at Stage 5. As we know (and as Dr. Suresh has mentioned earlier), Stage 3 patients are quite mild in severity but it can progress rapidly to Stage 4. Patients can deteriorate very quickly. When patients presented to us at Stage 3, this is the best time to alert the anaesthetist and our team to be more vigilant in terms of managing this group of patients.

Presenting Symptoms

The most common presenting symptom is shortness of breath. This is not surprising simply because when they come in at Stage 3, 4, and 5, the patients were already symptomatic. At the same time, they required supplemental oxygen. The other common symptoms are fever, cough, diarrhoea and vomiting. Other symptoms include myalgia and sore throat. Two of our mortality cases presented with anosmia.

Who referred the patients to COVID-19 hospitals?

Where did they come from? Majority of our mortality cases were referred from the government hospitals, followed by walk-in to the Emergency Department, referral from health clinics, private hospitals, district health office (*pejabat kesihatan daerah*, PKD), general practitioners (GP) clinics and quarantine centres.

Comorbidities

In terms of the risk factors, it is the same as what Dr Suresh has presented earlier. Majority of the cases came with underlying hypertension, followed by diabetes, coronary artery disease, dyslipidemia, chronic kidney disease, obesity, heart failure, malignancy and chronic liver disease. One of the deceased had underlying HIV. When we talked about other comorbidities, the patients were mostly immunocompromised and, on some medication, e.g. psoriasis, hypothyroidism etc.

When we look at the data, we can see that about 70% of the deceased had multiple comorbid (two or more comorbidities). Single comorbidity contributed about 24% and no comorbidity contributed 8.5%. When we talk about the deceased with no comorbidity, the majority of them presented to us late.

Smokers VS non-smokers

Based on our data, those from the deceased, non-smokers contributed about 79.5% while smokers contributed about 20.4%.

Descriptive statistics on Clinical Management

Number of Cases Managed in ICU

We have about 63% of the deceased which were managed in ICU, while approximately 21% were managed outside ICU. Bear in mind, during the initial stages, COVID-19 was (and still is) a new disease. Early days, the patients were intubated in a negative pressure room in the ward. With time and due to the rapid disease progression, we have learnt that we need to manage the patient by intubating and ventilating them in ICU. 13 patients from the 21% (whom were managed outside the ICU) were intubated, ventilated and managed in the negative pressure rooms in ward while 4 of them were brought in dead (BID) and 4 of them had do-not-resuscitate (DNR) order (as per requested by the family member and next of kin).

Treatment

Let’s look at the number of cases treated with hydroxychloroquine or chloroquine. Majority (about 80%) received hydroxychloroquine or chloroquine. The number of cases treated with both antivirals and antibiotics were around 90%. The other 10% came from patients who were BID and DNR.

Clinical Findings

In total, to date, we have 121 mortality cases. The committee has managed to review 70 patients' case files. Based on those 70 files, the majority of the issues are recurring, and they happened during the initial phase of the disease. Based on that, what we have found glaring was that most of the patients may look very comfortable at presentation. Hence, as mentioned by Dr Suresh earlier, the hypoxia state must be assessed not just based on capillary SpO_2, but also based on the exertional dyspnoea, laboratory parameters (e.g. ABG) and radiological findings (i.e. General appearance + clinical examination + laboratory & radiological findings). Most of the patients were in hypercoagulable state. Thus, DVT prophylaxis must be started early. Prompt anticipation of COVID-19 patient's deterioration status must be in place. The patients coming in with Stage 3 and above do require close monitoring. Therefore, early anaesthetic referral is deemed necessary especially once the patient requires intubation and ventilation in ICU

Other Findings

Effective Communication

We also looked into other things besides clinical management. This includes the communication issues between the management teams *(i.e.* emergency physician, physician, infectious disease physician, anaesthetist, intensivist). Effective communication between clinicians can prevent any delays in treatment and management.

Logistics Arrangement

Logistic arrangements for ICU care between COVID-19 and Non-COVID-19 hospitals need to be strengthened. This was the committee's first recommendation after the first meeting. We cannot pinpoint a single factor as to why the patient died, but we have to bear in mind that multiple factors including possibility of logistic delays do occur at the early phase of the disease management.

Early Referral

Early referral to the critical care team is essential especially for high risk groups like elderly/high risk patients with comorbidities regardless of the stage of presentation.

Recommendations

When we talk about recommendations, we are looking to improve the outcomes, reduce morbidity and mortality. At the same time, we are also looking at post MCO and future pandemic preparedness. Based on that, we have divided our recommendations into 3 subheadings: the structure, the process and the outcome.

Before we go into details, the involvement of the hospital administrators is the basic foundation of our recommendations. They must be involved in the management of COVID-19 especially in the morbidity and mortality (M&M) review discussion. As we know, it's not all about the clinical management, it's also about the administrative and the organizational process of the hospital that will allow us to provide the best quality of care for our patients. At the same time we need to enhance multi-disciplinary communication in managing COVID-19 patients, and working together as a team towards the same goal.

The Structure

To improve outcome, reduce morbidity and mortality

In terms of structure, we have proposed that:

1. To manage COVID-19 patients in the Intensive Care Unit (ICU) with negative pressure rooms. Hence, we must always ensure that an ICU bed is available for COVID-19 patient
2. Hospitals must prepare a Mortality Report within a week.
3. Systematic referral and systematic procedure when there is a need to transfer patients from one centre to another.

Post MCO and future pandemic preparedness

For the preparedness of future pandemic, post MCO, in terms of structure, our ICU should be equipped with negative pressure isolation rooms (ratio 1:4); proper logistics and resources management in terms of transferring COVID-19 patients; proper laboratory setups, and capacity building. The planning of capacity building of the sub-specialized training, especially for intensivists and infectious disease physicians must be in place.

The Process

To improve outcome, reduce morbidity and mortality

When we talk about the process, we must remember that we need full compliance with the usage of admission clerking sheets, clinical monitoring sheets and the guidelines of COVID-19 management. All these processes are in place with close collaboration with our infectious disease physicians, anaesthetist and hospital administrators. Therefore, the compliance to all these policies that we have put inline is a must.

Another important measure is the early referral to the critical care team for patients who are stage 3 and above, i.e. the elderly (aged 60+), pregnant lady, obese and/or patients with comorbidity.

Post MCO and future pandemic preparedness

For post MCO and future pandemic preparedness, we must remember that continuity of care in management of COVID-19 patients is a very important aspect. We also need to ensure that there is an adherence to the utilization of personal protective equipment (PPE) and guidelines. In the future, we might need to consider using mechanical cardiopulmonary resuscitation (CPR) for infectious disease patients.

The Outcome

To improve outcome, reduce morbidity and mortality

In terms of outcomes, we need to improve the clinical documentation and records of our monitoring and clinical examination findings such as respiratory rate, exertional dyspnoea, SpO_2 monitoring etc. DVT prophylaxis for COVID-19 patients must be given early. A standardized blood investigations parameters especially tests that will indicate the patient's status from time to time (like what Dr.Suresh has mentioned earlier: CRP and serum ferritin) must be carried out.

Post MCO and future pandemic preparedness

In terms of future pandemic preparedness, we need to develop a guideline for DVT prophylaxis for COVID-19 patients and I believe this is a work in progress by our intensivists. Revision of standard operating procedures (SOP) and guidelines from time to time must be carried out due to the fact that this is a new disease and there are still many things that can be discovered. Thus, our SOPs and guidelines must be revised when there are new updates.

We also need to focus on research and publication, especially when we do know that COVID-19 is a new disease. It is also important to have continuous education and awareness of COVID-19. Nevertheless, we should use post-mortem as a tool to understand the disease and progression of illness, and to answer medical questions arising from COVID-19.

The Directives from the COVID-19 Mortality Review Committee

COVID-19 Admission Clerking Sheet

I would like to share with you some of our directives. We had our first meeting on the 28th March 2020, and we came up with our first recommendation on the implementation of the COVID-19 Admission Sheet (that we developed together with our infectious disease physicians) on the 30th March 2020. It has been circulated since 30th March 2020 for the usage of the hospitals.

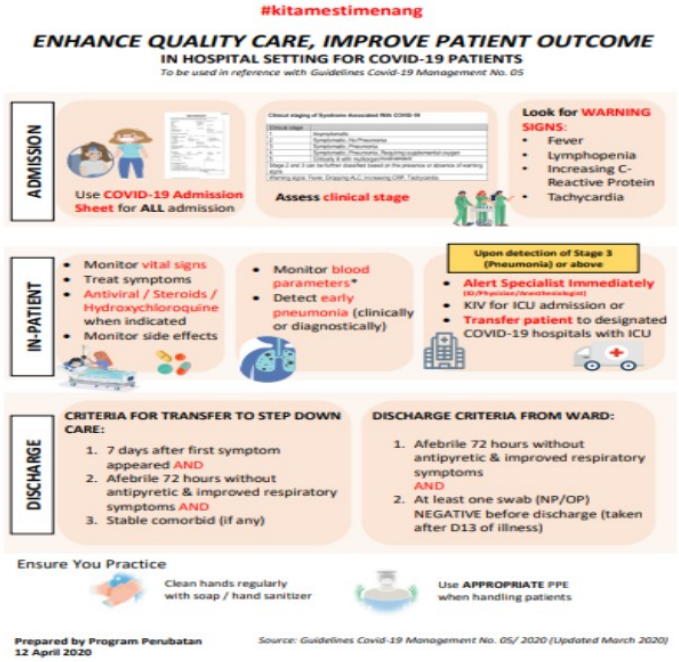

Diagram 21: Infographics on recommendations to enhance quality of care and improve patient outcome in hospital setting for COVID-19 patients.

On the 12th of April 2020, we came up with an infographic together with the CPRC Hospital Services, which includes the recommendations related to the quality of care and improvement in hospital setting for COVID-19 patients.

Continuous Surveillance Letters from the Deputy Director General of Health (Medical) Malaysia

Many letters have been written; this includes the continuous surveillance letter. The two most important letters came from the Deputy Director General of Health (Medical) Malaysia, where the letters were on the directives of continuous monitoring and surveillance of COVID-19 management.

Based on the new COVID-19 guidelines which was released by WHO on the 16th April 2020, we have asked the hospital for the reclassification of the cause of death, letter dated 8th May 2020. The reclassification emphasized on whether the patient died **because** of COVID-19, or the patient died **with** COVID-19. At the same time, on the 12th May 2020, we have also circulated another letter to the hospital to carry out their own mortality review on COVID-19 deaths at the hospital level.

Summary

In summary, the committee hopes that our recommendations will be taken into consideration. Having said that, the majority of our recommendations have been in place. This is important to ensure the best outcome and the highest quality of care is being delivered to our patients. The recommendations must be carried out in synchronization with the clinical team in the management of COVID-19 patients. The findings and data which have been generated should be combined with our clinical data, to ensure the overall improvements can be carried out systematically.

For your information, The National COVID-19 Mortality Review Committee in collaboration with the Institute for Clinical Research (ICR), National Institute of Health (NIH), Dato' Dr. Goh Pik Pin's team is coming out with our first paper on mortality review sometime next week.

With that, thank you.

Acknowledgement:

Datuk Dr. Rohaizat bin Yon
Dato' Dr. Goh Pik Pin
Dr. Woon Yuan Liang
Dr. Salwa Rohaznita bt Abd Wahab
Dr. Nurul Shahida bt Mohd Saffe

Q&A Session

1. Could you talk about drug therapy in COVID-19, namely about the withdrawn paper on hydroxychloroquine (Lancet) and the usage of dexamethasone? Initially WHO has advised us not to use steroids upfront. What is your comment on this?

Dr. Suresh: We disagree with the remarks on "hydroxychloroquine causing higher mortality". We do not think that this happened, as we were monitoring our cases closely, and we do serial ECG. By now, we know that the claims on hydroxychloroquine were based on faulty data set associated with the company Surgisphere Corporation (referring to the retracted faulty papers in the Lancet and New England Journal of Medicine (NEJM)). There were never that many arrhythmia or cardiac deaths in hydroxychloroquine arm. In Malaysia context, we will be publishing our data soon. Overall, we have not seen that many cardiac complications due to hydroxychloroquine.

With regard to steroids, just to be fair, WHO have stated that there is no evidence for steroids yet, which is right. In addition, WHO has also mentioned that in SARS, steroids did harm when used in influenza patients. That is the reason they are not keen on the usage of steroids. However, earlier on, we had seen with our own experience and after hearing from the Chinese and the Italian's experiences in managing COVID-19 patients, we started using steroids at the end of March 2020 for a selected group of patients for cytokine release syndrome, and we have been using it since then, as a standard of care on our side.

Datuk Dr. Christopher: In relation to what Dr. Suresh has mentioned, I think COVID-19 also tells us how careful we must be in sending out papers for publication. I think that our robustness in reviewing papers for publication, we cannot let off guard, and here, because there is a need to get data to be out fast, I think many journals let loose in that particular area. They became more relaxed in that area. Now that we could look back at things, we wonder, how did we make hydroxychloroquine become our norm for all cases. That is a good example for us not to follow again.

2. In the previous webinar, it was mentioned that adolescents are more likely to have Kawasaki Disease like illness (MIS-C). Do we see such characteristics among patients older than 12 years old and young adults?

Dr. Suresh: I don't think we have seen one so far, but I think it is a rare manifestation and lucky for us, we did not have that many patients who were infected in that age group in the country. We have not seen one so far, and I am not surprised as it is a rare manifestation.

Datuk Dr. Christopher: As Dr. Suresh have mentioned, I think the number of paediatric cases are very small. We won't be the country to look for such cases. It is good to be aware of such condition.

3. We know that in the later part of our national COVID-19 mortality committee, we brought in forensic colleagues to help the committee. Dr.Faizah, can you share with us, (clearly we are not doing post-mortem for every case), going forward, what is the game plan for the Ministry of Health in terms of when do we do post-mortem among COVID-19 cases who may passed away in the future?

Dr. Faizah: Thank you, Datuk Dr. Christopher for the question. Based on the last discussion with the Forensic Team at the National Crisis Preparedness and Response Centre (CPRC) meeting, we will proceed with postmortem for the unknown deaths and for BID cases. We do not consider postmortem for every patient. Perhaps for patients who died at a very young age, we might consider those cases for postmortem. This is the decision.

4. What is your comment of the types of COVID-19 in South East Asia based on Cambridge scientists?

Dr. Suresh: I am sorry, I am not well versed with the different COVID-19 strains that are affecting different parts of the world currently.

Datuk Dr. Christopher: Not something we are looking into at the moment, to be frank. Maybe the researchers in the Institute for Medical Research (IMR).

5. Are there any COVID-19 cases in Malaysia or abroad that affect patients with haemoglobinopathies such as thalassaemia or sickle cell?

Dr. Suresh: Offhand, I can't remember any case of a patient with thalassaemia. As for sickle cell disease, of course, it is very rare in Malaysia. Offhand, I cannot think of a thalassaemia patient with COVID-19 right now but I may miss one of them.

6. What is the panellists' view on using hydroxychloroquine (HCQ) at an early stage of COVID-19 infection that might reduce the severity of COVID-19 patients? WHO withdrew HCQ arm.

Dr. Suresh: We were hoping that when we started hydroxychloroquine in the early stage of the disease, hydroxychloroquine could prevent severe disease. The preliminary data of our data set, before and after study, with historical cohorts, have told us that hydroxychloroquine did not reduce the severity of COVID-19 patients. Our study is not powered enough. It can only pick up to 18% difference, anything less than 18% difference it cannot be picked up. The more definite study would be the study conducted by National Institutes of Health which would be published soon. Currently, there is no data that says hydroxychloroquine reduces the severity of COVID-19 patients.

7. What is your opinion on WHO withdrawing the recruitment of patients for hydroxychloroquine treatment in trial?

Dr. Suresh: We had some discussion yesterday, and I think that the WHO preliminary data also showed that there was no advantage of hydroxychloroquine, as compared to placebo. I also think that they are in the process of withdrawing that arm from future studies.

8. We hope there is no second surge of COVID-19, but as DG of Health has mentioned many times, we are preparing for any possibilities. In terms of the clinical setup, will there be a change in the way we set up our clinical services for COVID-19? As you know there are some COVID-19 hospitals like Sungai Buloh Hospital, and we have hybrid hospitals. Going forward, will there be change in how we deal with COVID-19 in the future, in terms of health care delivery?

Dr. Faizah: To be honest, at the Medical Development Division, we have already prepared a few guidelines and standard operating procedures (SOP) on how we are supposed to see our patients and operate on a daily basis, based on the needs to protect our healthcare workers and our patients. Basically, we need to break the chain of COVID-19 transmission. Everything was in place before Dr.Rohaizat retired.

We have already distributed all the guidelines, the SOPs and the policies to the hospitals. At this point of time, the things we do from COVID-19 hospitals to hybrid hospitals and non-COVID-19 hospitals, the transition has been quite smooth, I must say. Although I can't deny the fact that there have been some hiccups on the ground level, at the same time, we are trying to do our best in order to facilitate our hospitals. Under the medical program, we are looking very hard and very detailed into it.

Everything is in place. This is actually in the best interest of protecting our healthcare workers and our patients.

There are a lot of changes in terms of how we deliver our care to patients, not just about promoting video telehealth consultation. We also ensure that our hospital practices the 3Ws and the 3Cs. (MOH's avoid the 3C and practice the 3W: Avoid 3C=Crowded places, Confined space dan Close conversation and practice 3W=Wash, Wear dan Warn).

9. We are all happy to see the data on COVID-19 patients' recovery using dexamethasone, as it is easy accessed to. Obviously, tocilizumab also has good data coming forward. Are you aware of any studies which compare these two drugs head-to-head?

Dr. Suresh: I think some centres, such as Hospital Sungai Buloh, Hospital Tuanku Jaafar in Seremban, and University of Malaya Medical Centre have an ongoing study which compares methylprednisolone and tocilizumab. We are starting the medications on patients with Category 4 disease. Our aim is to see whether it can prevent intubation. Lucky for us, we don't have any patients we can recruit into the study yet, but that would be something that we want to study for now.

10. Are patients on Disease-modifying anti-rheumatic drugs (DMARDs) and long term steroids less likely to get cytokine release syndrome?

Dr. Suresh: We don't know yet as we don't have enough patients in this group yet. I have not seen a single patient on DMARDs who has COVID-19 so far. Maybe this group of patients are being very careful in maintaining social distancing. So we don't know that yet.

11. What are the mortality numbers involving healthcare workers?

Dr. Suresh: First and foremost, 52 of our frontliners had COVID-19. Approximately 21% developed COVID-19 from the community. Only 18% of our frontliners were COVID-19 positive due to contact with patients. There were a small number of frontliners who contracted COVID-19 from other groups.

Secondly, we conducted an antibody study involving approximately 400 frontline workers who are managing COVID-19 patients in Hospital Kuala Lumpur and Hospital Sungai Buloh. We didn't find anyone who has COVID-19 antibodies. I think there were 2 frontliners who passed away due to COVID-19. If I recalled correctly, one came from Johor, while one came from Perlis.

Dr. Faizah: Yes, there were 2 deaths among healthcare workers, one is from Johor while one is from Perlis. Both healthcare workers did not contract the illness from patients. They contracted it from the community and not during work routine.

12. Are we going to use convalescent plasma in Malaysia?

Dr. Suresh: Convalescent plasma is available in Malaysia. We have collected and kept it. With so much data and so many drugs available, we have not used one yet, but we have it, if we are required to use it.

13. Can you update us on the sequencing of the virus strains? Were there mutations? Will it affect the pick up rate of RT-PCR? Any updates from the Institute for Medical Research (IMR)?

Dr. Suresh: I do not have data on sequencing of the virus strains and mutations. Maybe we should ask NIH whether they would consider another update on these issues from IMR on a later date.

Datuk Dr. Christopher: We did hear from IMR that they might be doing this. You might find some changes in the sequencing of the virus strains, which does not mean that it is a sustained mutation. I think this is a good idea, maybe Dr. Goh can pass the message to the IMR side, to find the right time to talk about this as well.

14. What are the common pitfalls that we picked up from the mortality review?

Dr. Faizah: The common pitfalls that we picked up from the mortality review was of course, during the monitoring part. This happened during the initial phase of the disease outbreak. We are talking about somewhere in March 2020 to early April 2020. Subsequently, after that, everything seems to be in place. As you can see from our graph, everything has come down and become plateauing. It reflects a lot on the aggressiveness of our management on the ground. The common pitfall is actually the monitoring at the initial phase and the awareness of people, as in they need to come in early. As we progress from March 2020 to April 2020 and May 2020, our community is more aware of the disease. Subsequently, we detected the disease at the early stage of presentation and early admission. So, I guess that is the reason why we are doing quite well at this point of time.

Datuk Dr. Christopher: Despite initial problems with PPE, our guidelines have addressed enough in terms of infection control issues with COVID-19. I think that we should be comfortable enough with that. As we prepare for the second surge, perhaps we can probably deal with things even better, going forward. We are pretty okay in that area, but the most important thing is whether compliance/adherence is adequate and our healthcare workers are adequately trained, and are equally motivated to do that now. The fear from many of us is that as our numbers drop (*i.e.* happens in all types of outbreaks such as dengue), all of us get a bit complacent. All of us would think that we no longer have to wash our hands frequently, we no longer have to wear this or wear that as nothing would happen anyway. I hope nobody becomes the first case because of that. I think as the leaders and heads of services on the ground, we need to maintain how important this is. COVID-19 is still a very deadly disease, when we look

at the world figures, more than 400,000 patients have died from this disease around the world.

15. Could you comment on the false positives on RT-PCR testing?

Dr. Suresh: it is tricky to say what false positive results are, because as you remember, COVID-19 diagnosis requires RT-PCR testing. RT-PCR testing is the gold standard. When the results are positive, but the patient turned out not to have any symptoms of COVID-19, this is okay as many people are asymptomatic. If no one else aside from the patient "gets" the disease, then the question would be if it is a false positive or not. We are picking up people towards the "tail end" of the disease, at Day 13 or Day 14 of the illness. At that point of time, RT-PCR can have low values, and that could be of 1 possibility.

The second possibility that I would want to point out is the statistical stuff, whenever we have a disease that is very rare, even though the sensitivity and specificity of the tests would be good, the positive predictive value will drop, the chances of false positives would become high. As the incidence of COVID-19 in our country becomes lower, the positive rate of any diagnostic tests will drop. This is something that we cannot run away from. Obviously, we need to put clinical and epidemiology data all together to determine the value of any test result.

Datuk Dr. Christopher: As Dr. Suresh has mentioned, RT-PCR is a very sensitive test. If the samples are taken adequately, false positive results probably would not happen that often unless there is a significant contamination at the laboratory levels. Since the SOPs are already out, this probably doesn't happen very often. False negatives are a whole different ball game, depending on when we take the test, and how the specimen was taken etc. As Dr. Suresh has also mentioned, when the numbers in the community drops, how sensitive the test will be impacted upon. Therefore, things would change. The question is, if the patient has a high risk for COVID-19 with symptoms consistent to COVID-19, and if a negative test result was obtained, we need to conduct the test again. This is a given thing, and it has to be the case.

“Wrap Up Message” by Datuk Dr Christopher Lee

Firstly, I would like to thank the 2 speakers, Dr. Suresh and Dr. Faizah for their excellent and clear presentation. Clearly, it tells us how far we have come. 5 months ago, we were preparing for a pandemic that is a true pandemic. H1N1 was a false pandemic if you can argue the case. This is for real, because we have seen the mortality rates, it was shocking, and we know how fast it spreads. In the last 5 months, we have found a way to deal with it. In terms of prevention, we know what works. We know that social distancing, hygiene especially hand hygiene, and surface disinfection at the right times work. I strongly believe masking works as well, especially in a confined space where we cannot practice any social distancing.

In terms of treatment, there has been significant progress. Even hydroxychloroquine may not work so well, to me, this is also progress. We are not using it as much now, and as Dr. Suresh has mentioned in the guidelines from the Ministry of Health, we have sort of dropped it in the initial recommendation of treatment for COVID-19. Over the last 4 or 5 months, we now have good data on Remdesivir, a drug that we do not have free access yet in this country, but I guess, it will come soon, just that it might take a bit longer. We are not completely helpless. We have antivirals that we have repurposed such as Kaletra that we can use for that, we have interferon and Favipiravir as well which is actually an anti-influenza drug. This is something that we can do. Now, we understand the way to use immunomodulators, and dexamethasone is not expensive.

This is an important message to say that when a patient is admitted, it is not just for isolation, there are some things that we can do for them. As mentioned by Dr. Suresh and as seen clearly in our mortality reviews, many patients, especially during the early outbreak in Malaysia, many of them came in very late. The moment they came in, they were at Stage 4 and Stage 5 of the disease. The doctors on the ground were struggling with it.

This is an important message for us as healthcare providers and other stakeholders must share with the population. If you have symptoms, you need to come forward early enough. We hope that the testing platforms would be fast enough, broad and wide enough, so that we can pick cases up early, and we can proceed to management earlier. We can safely say that there are some treatments we know that can work. This is the important message.

With that, I would like to wrap up today's session. Once again thank you to both speakers, Dr.Suresh and Dr.Faizah for the excellent presentation. Thank you to Dato' Dr. Goh as usual. And I would like to thank everyone who has joined us in this session today.

Speakers' Brief Bio

Dr. Suresh Kumar Chidambaram is the Head of Medical Department, Infectious Diseases Consultant in Hospital Sungai Buloh. He has been Infectious Diseases Consultant in Hospital Sungai Buloh since 2003. He is also a visiting consultant for the National Heart Institute (IJN).

Hospital Sungai Buloh is a full COVID-19 hospital and has been in the forefront of the COVID-19 response in the country. He also sits in the national task force that spearheads the national response.

He has participated in several international HIV treatment trials and has served on expert panels for national treatment and practice guidelines relating to infectious diseases including HIV, Dengue, Adult Immunization and National antibiotic guidelines. Dr Suresh is actively involved in the Infectious disease's fellowship programme in the country. He is the Past President of the Malaysian Society for HIV Medicine, MASHM.

Dr. Faizah Muhamad Zin is the Head of Clinical Audit Unit, Medical Care Quality Section, Medical Development Division, MOH Malaysia. Dr. Faizah graduated from University Putra Malaysia in 2004 and studied Community Health Medicine in National University of Malaysia. She has been working in the Ministry of Health for the past 16 years. The Clinical Audit Unit is in charge of Clinical Audit Activity of the Medical Programme, implementation of Pain as 5th Vital Sign and Pain Free Programme, Perioperative Mortality Review (POMR) and COVID-19 Mortality Review.

Datuk Dr. Christopher Lee Kwok Choong is an Infectious Disease Consultant and the former (retired) Deputy Director General of Health (Research & Technical Support) in Ministry of Health Malaysia with vast experience in managing infectious disease including SARS pandemic. He has trained many infectious disease (ID) physicians in Malaysia. He is also the chairman of the National COVID-19 Mortality Review committee.

Click the link below to view the panellists' information and details of the webinar:
https://clinupcovid.mailerpage.com/resources/s9v7c4-covid-19-mortality-review-in-mala

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