به نام خدا

Covid 19 & DM

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
- What are the cause of hyperglycemia in covid-19?
- How glycemic control can influence COVID mortality?
- What are the glycemic target in COVID patients?
- What are the effective treatments in out patients & hospitalized patients?
- How should GIH be managed?
- What is the prognosis of DKA in covid-19
- How should DKA be prevented/treated?

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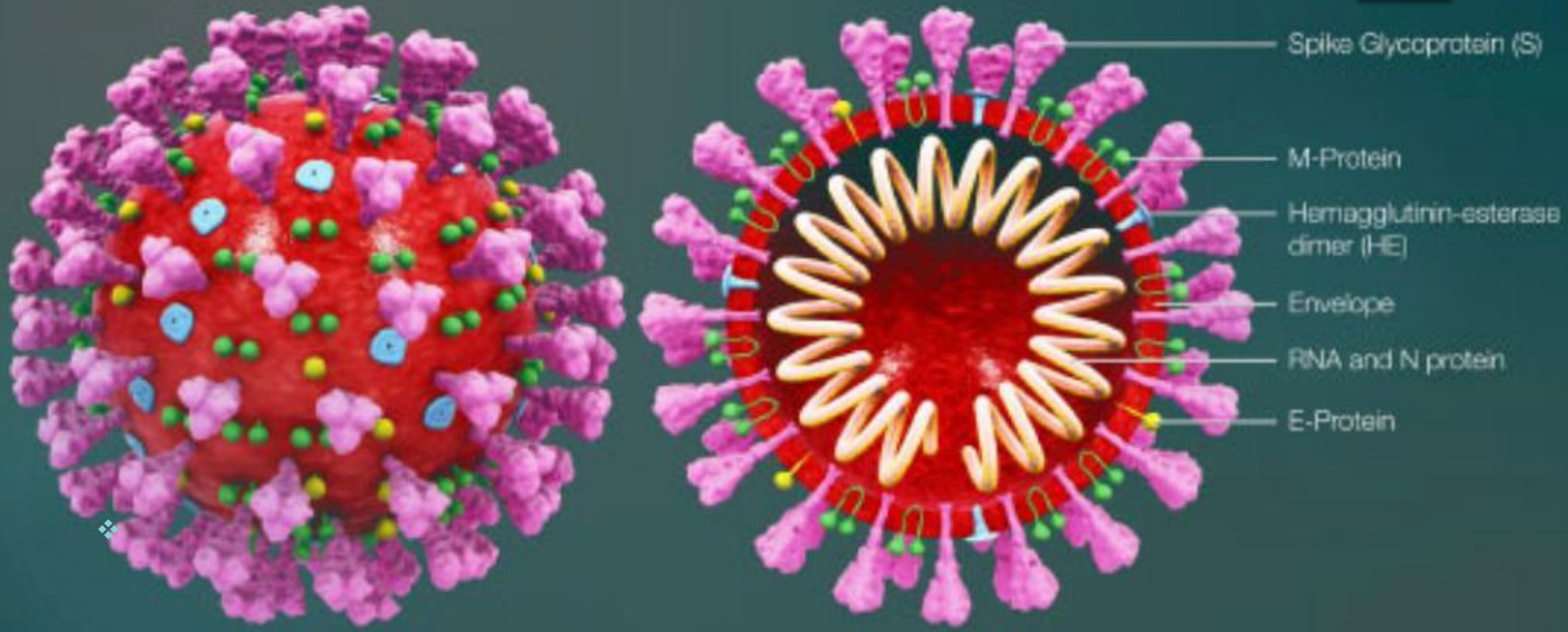
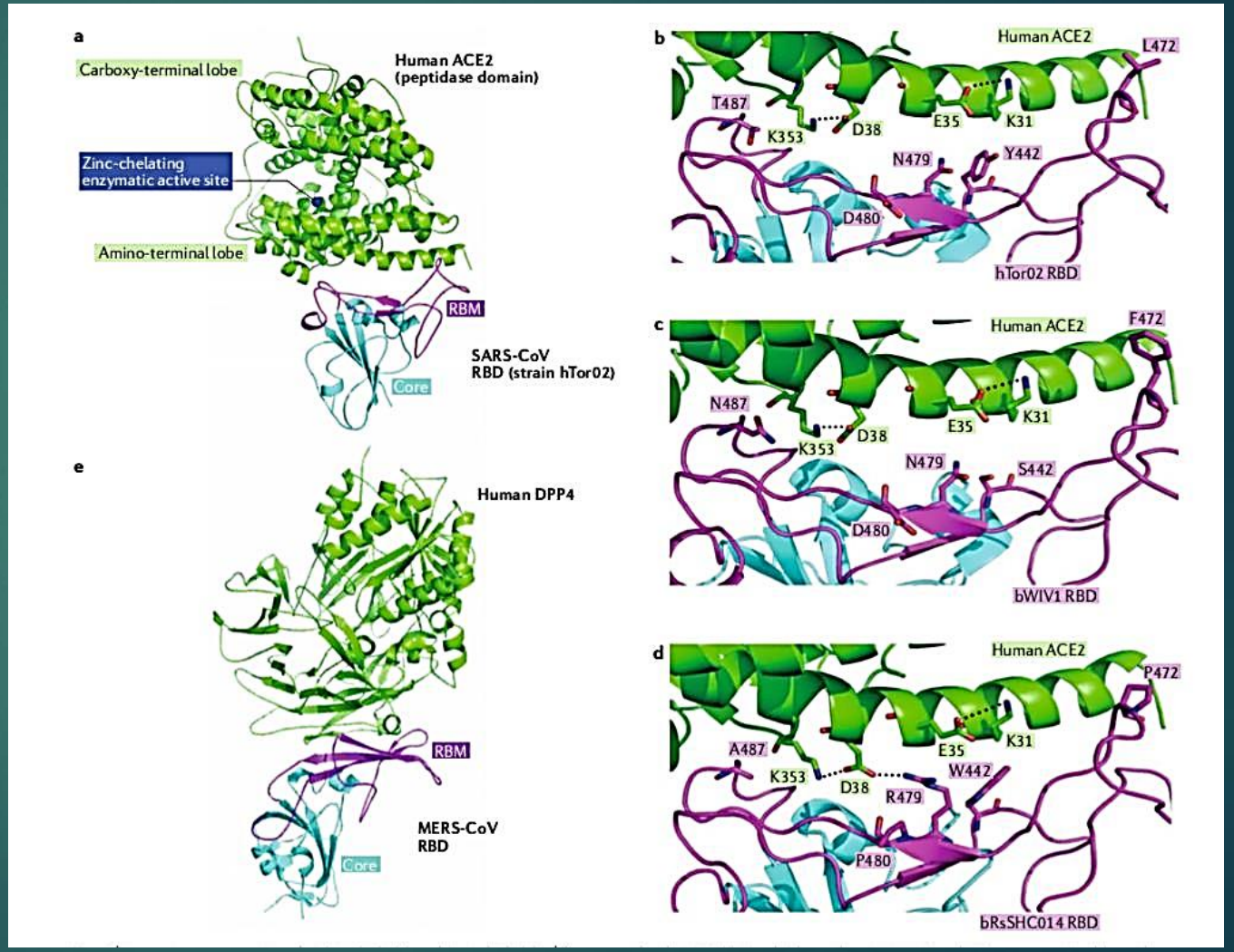
COVID 19:enveloped viruses, single-stranded , positive sense RNA genome , respiratory infection in human.



Origin and Evolution of Pathogenic Coronaviruses .NATURE REVIEWS

Coronaviruses

- Main entry receptor is ACE2
- ACE2 receptor is expressed in alveolar lung cells , cardiac myocytes , vascular endothelium, pancreas.
- DPP4 co-receptor



Corona viruses

- Covid patients developed symptoms at 5-6 days after infection
- Mild symptom in initial stage for 2 weeks
- Sever illness, ARDS , multi-organ involvement ,shock
- High risk covid patients:

  advanced age

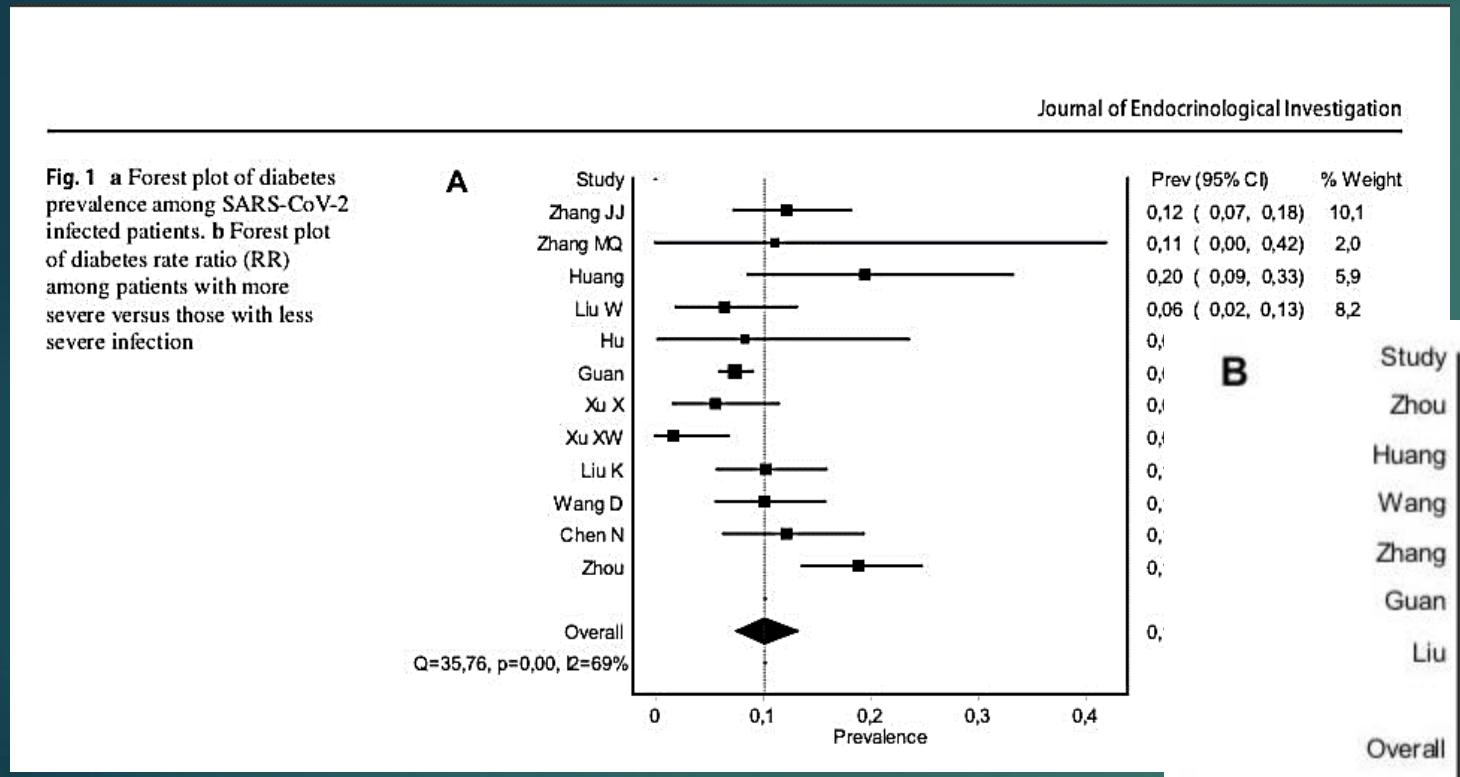
  Male sex

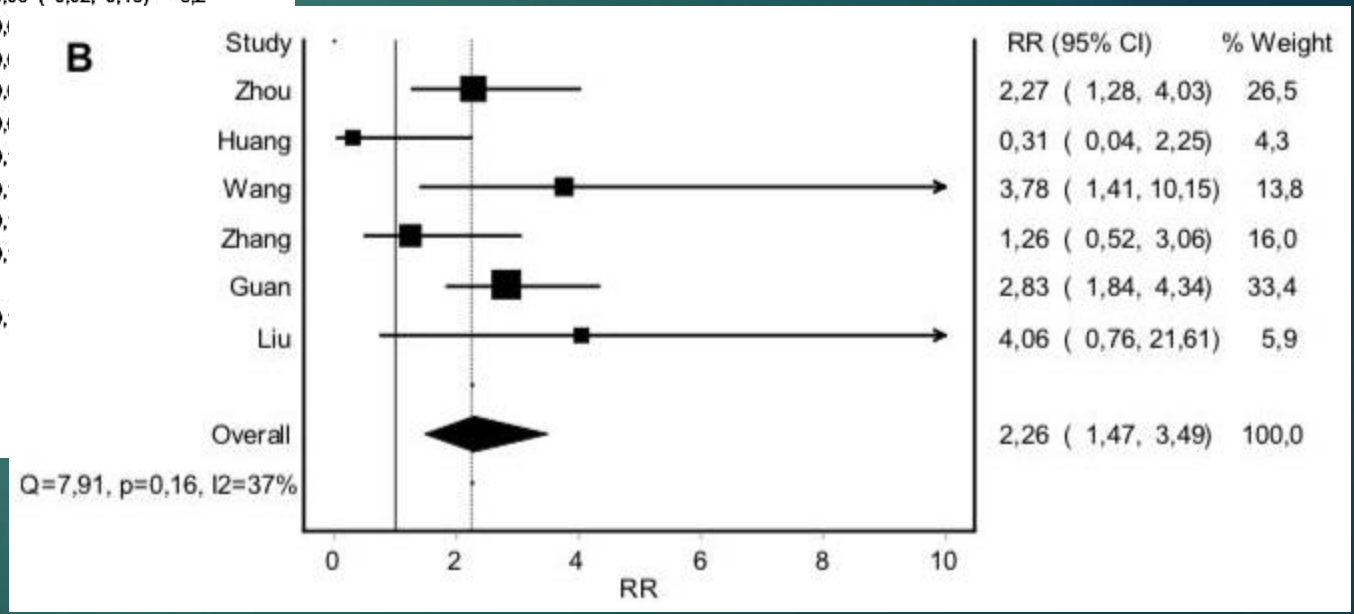
  CVD

  Obesity

  T1DM,T2DM

Prevalence of DM among people infected with covid-19





Prevalence and Impact of Diabetes Among People Infected with SARS-COV-2.Journal of Endocrinological Investigation(2020)

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 395–403

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression☆

Ian Huang, Michael Anthonius Lim, Raymond Pranata*

Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

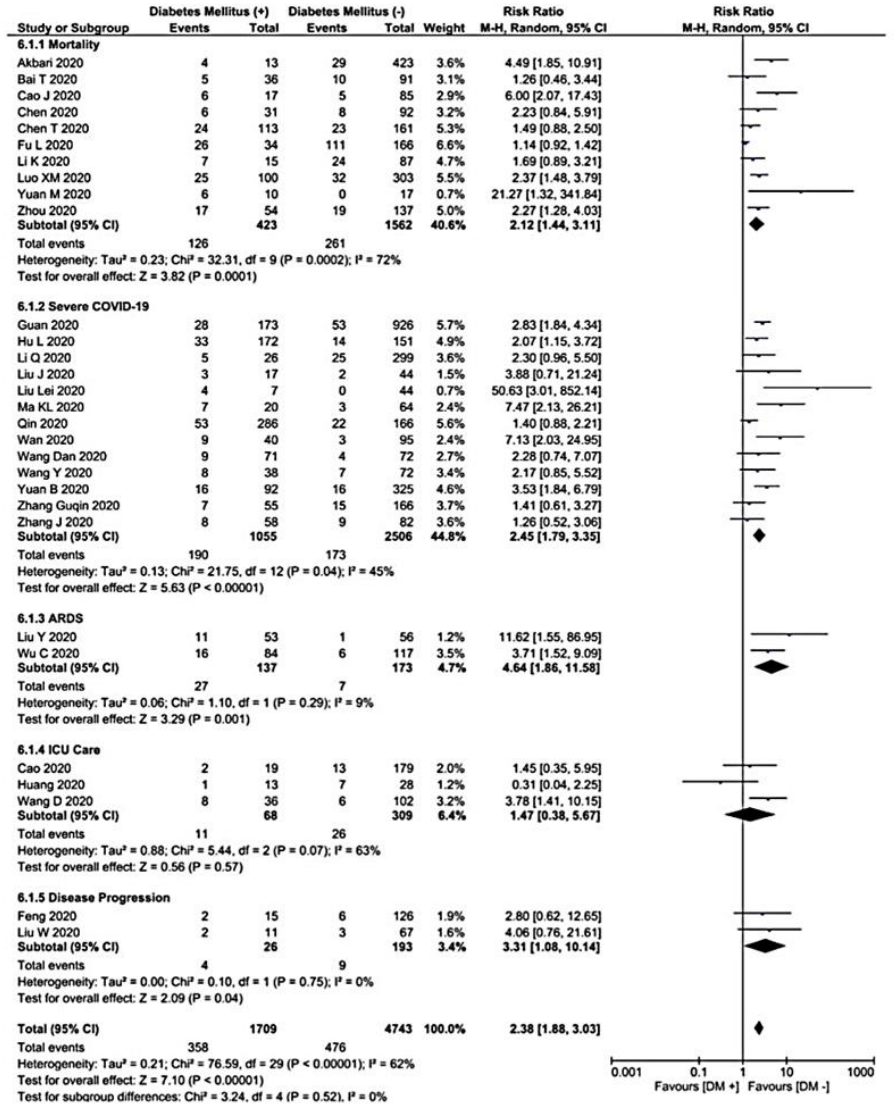
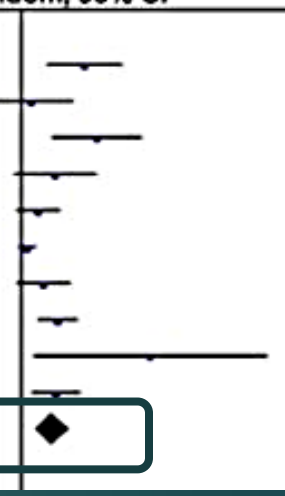


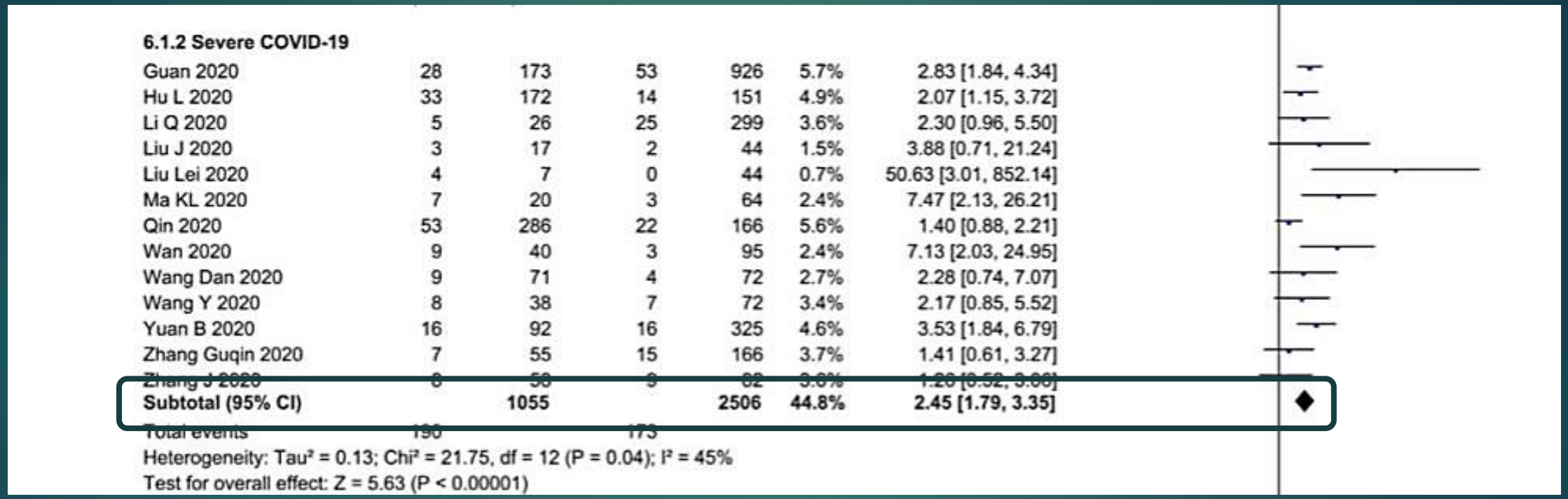
Fig. 2. Diabetes Mellitus and Poor Outcome. Forest-plot shows that diabetes mellitus was associated with increased composite poor outcome and its subgroup which comprises of mortality, severe COVID-19, ARDS, need for ICU care, and disease progression in patients with COVID-19. ARDS: Acute Respiratory Distress Syndrome, COVID-19: Coronavirus Disease 2019, ICU: Intensive Care Unit.

Covid19 mortality in diabetic patients

Study or Subgroup	Diabetes Mellitus (+) Events	Total	Diabetes Mellitus (-) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Mortality						
Akbari 2020	4	13	29	423	3.6%	4.49 [1.85, 10.91]
Bai T 2020	5	36	10	91	3.1%	1.26 [0.46, 3.44]
Cao J 2020	6	17	5	85	2.9%	6.00 [2.07, 17.43]
Chen 2020	6	31	8	92	3.2%	2.23 [0.84, 5.91]
Chen T 2020	24	113	23	161	5.3%	1.49 [0.88, 2.50]
Fu L 2020	26	34	111	166	6.6%	1.14 [0.92, 1.42]
Li K 2020	7	15	24	87	4.7%	1.69 [0.89, 3.21]
Luo XM 2020	25	100	32	303	5.5%	2.37 [1.48, 3.79]
Yuan M 2020	6	10	0	17	0.7%	21.27 [1.32, 341.84]
Zhou 2020	17	54	10	127	5.0%	2.27 [1.28, 4.03]
Subtotal (95% CI)		**423**		**1562**	**40.6%**	**2.12 [1.44, 3.11]**
Total events	126		281			



Covid 19 sever disease in diabetic patients

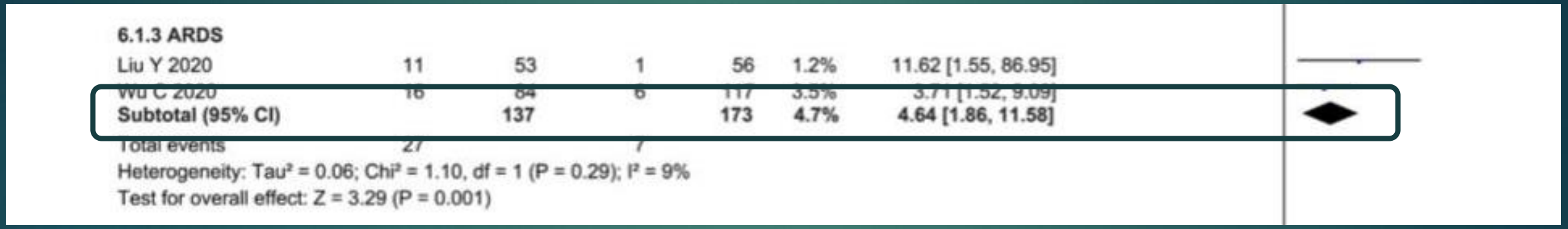


6.1.2 Severe COVID-19						
Guan 2020	28	173	53	926	5.7%	2.83 [1.84, 4.34]
Hu L 2020	33	172	14	151	4.9%	2.07 [1.15, 3.72]
Li Q 2020	5	26	25	299	3.6%	2.30 [0.96, 5.50]
Liu J 2020	3	17	2	44	1.5%	3.88 [0.71, 21.24]
Liu Lei 2020	4	7	0	44	0.7%	50.63 [3.01, 852.14]
Ma KL 2020	7	20	3	64	2.4%	7.47 [2.13, 26.21]
Qin 2020	53	286	22	166	5.6%	1.40 [0.88, 2.21]
Wan 2020	9	40	3	95	2.4%	7.13 [2.03, 24.95]
Wang Dan 2020	9	71	4	72	2.7%	2.28 [0.74, 7.07]
Wang Y 2020	8	38	7	72	3.4%	2.17 [0.85, 5.52]
Yuan B 2020	16	92	16	325	4.6%	3.53 [1.84, 6.79]
Zhang Guqin 2020	7	55	15	166	3.7%	1.41 [0.61, 3.27]
~~Zhang J 2020~~	~~8~~	~~58~~	~~9~~	~~82~~	~~3.6%~~	~~1.20 [0.52, 3.06]~~
Subtotal (95% CI)		**1055**		**2506**	**44.8%**	**2.45 [1.79, 3.35]**
Total events	190		173			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 21.75$, df = 12 (P = 0.04); $I^2 = 45\%$

Test for overall effect: Z = 5.63 (P < 0.00001)

Covid19 ARDS in diabetic patients



6.1.3 ARDS							
Liu Y 2020	11	53	1	56	1.2%	11.62 [1.55, 86.95]	
Wu C 2020	16	84	6	117	3.5%	3.71 [1.52, 9.09]	
Subtotal (95% CI)		**137**		**173**	**4.7%**	**4.64 [1.86, 11.58]**	
Total events	27		7				

Heterogeneity: Tau² = 0.06; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%

Test for overall effect: Z = 3.29 (P = 0.001)

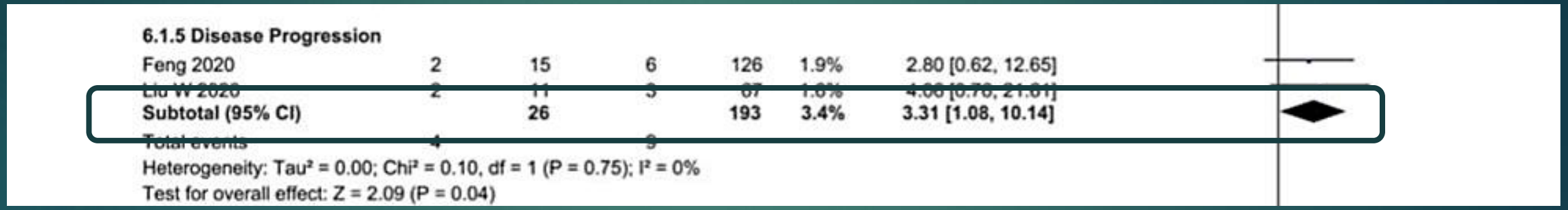
ICU admission in diabetic patient

6.1.4 ICU Care						
Cao 2020	2	19	13	179	2.0%	1.45 [0.35, 5.95]
Huang 2020	1	13	7	28	1.2%	0.31 [0.04, 2.25]
~~Wang D 2020~~	~~8~~	~~36~~	~~6~~	~~102~~	~~3.2%~~	~~3.78 [1.41, 10.15]~~
Subtotal (95% CI)		**68**		**309**	**6.4%**	**1.47 [0.38, 5.67]**
~~Total events~~	~~11~~		~~26~~			

Heterogeneity: $Tau^2 = 0.88$; $Chi^2 = 5.44$, df = 2 (P = 0.07); $I^2 = 63\%$

Test for overall effect: Z = 0.56 (P = 0.57)

Covid 19 progression in diabetic patients



6.1.5 Disease Progression						
Feng 2020	2	15	6	126	1.9%	2.80 [0.62, 12.65]
Liu W 2020	2	11	3	67	1.6%	4.06 [0.76, 21.61]
Subtotal (95% CI)		**26**		**193**	**3.4%**	**3.31 [1.08, 10.14]**
Total events	4		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Test for overall effect: Z = 2.09 (P = 0.04)

questions

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Risk factors of covid related mortality in diabetic patients

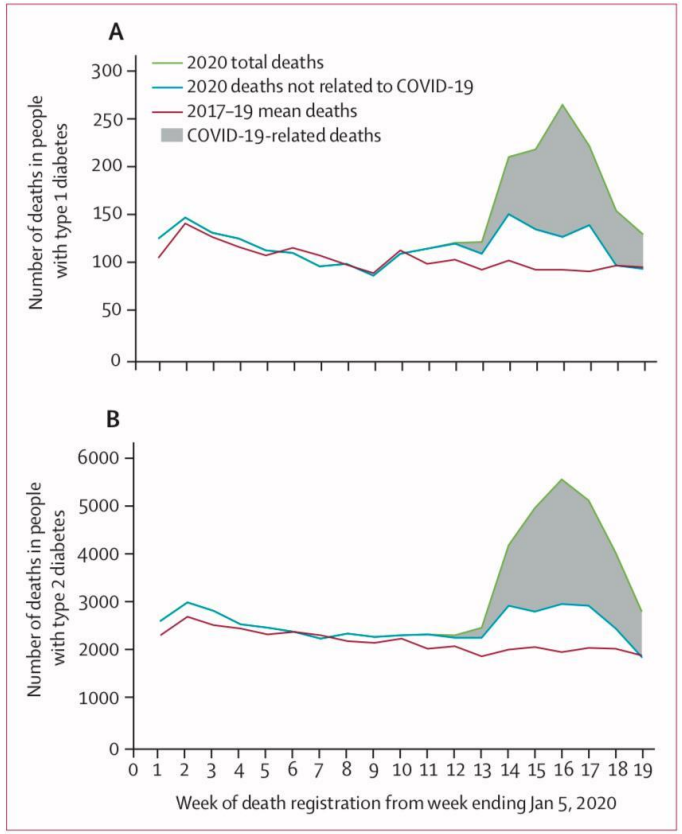
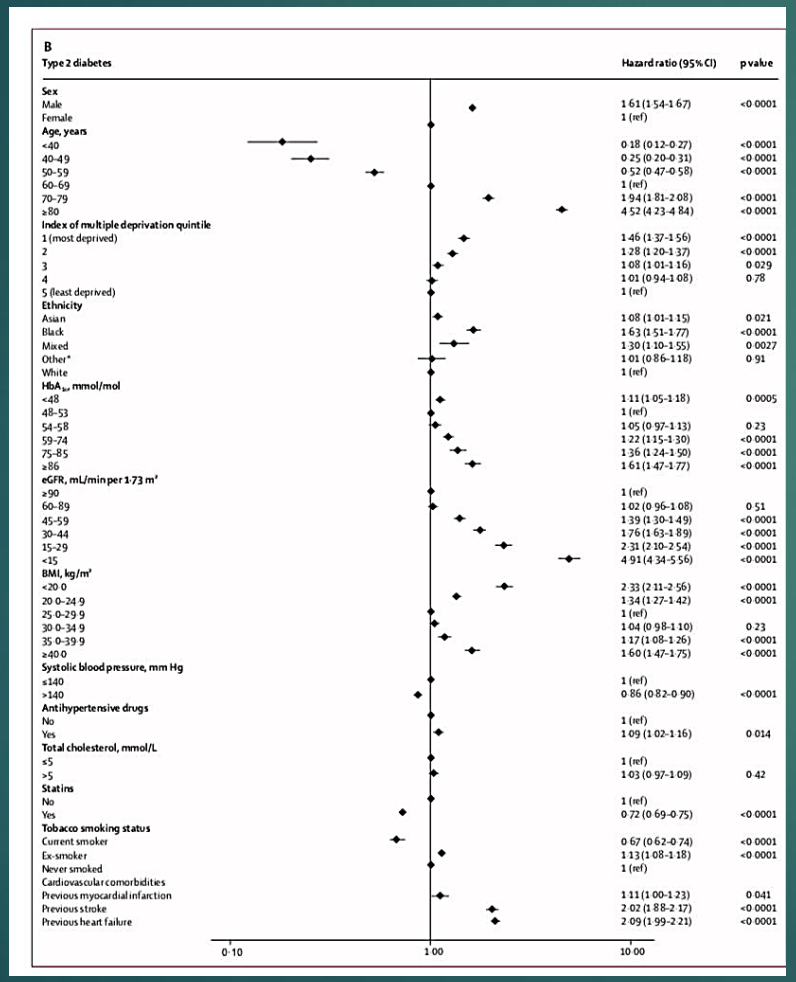


Figure 1: **Weekly numbers of deaths registered from week 1 to week 19 in people with type 1 (A) and type 2 (B) diabetes in England, 2017–19 and 2020**

Deaths in 2020 are stratified into COVID-19-related deaths and deaths not related to COVID-19.

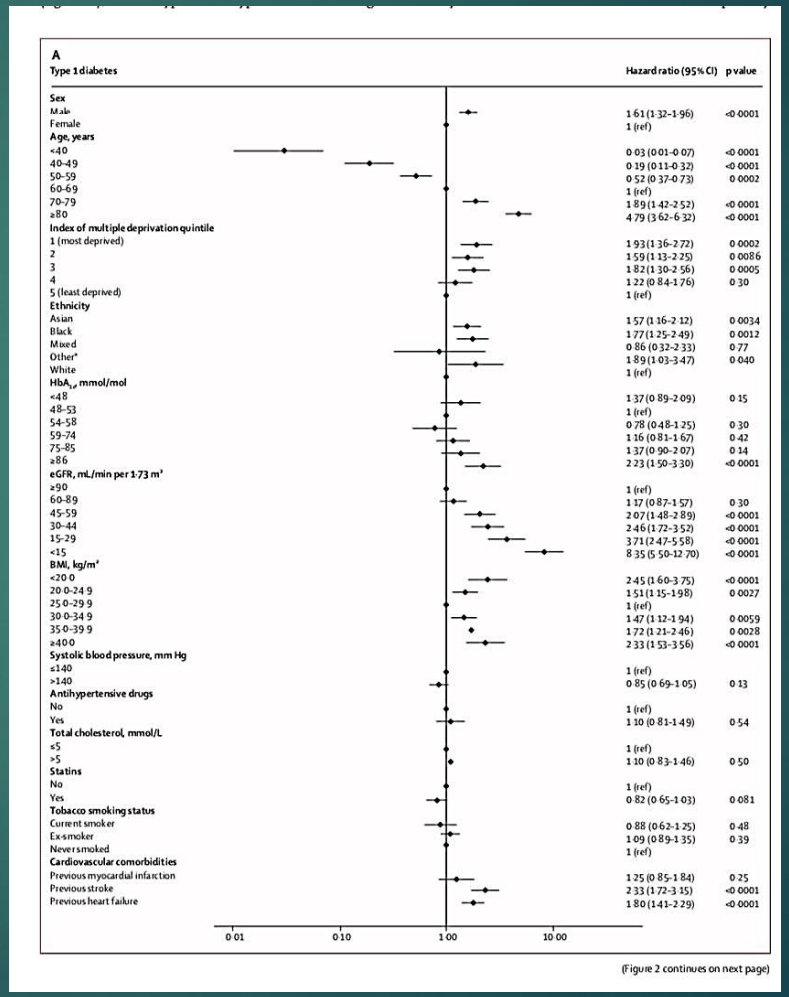
Risk Factors for COVID-19-related Mortality in People with Type 1and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

Adjusted hazard ratios for COVID19 death in people with DM type 1&2



B Type 2 diabetes	Hazard ratio (95% CI)	p value
Sex		
Male	1·61 (1·54–1·67)	<0·0001
Female	1 (ref)	
Age, years		
<40	0·18 (0·12–0·27)	<0·0001
40–49	0·25 (0·20–0·31)	<0·0001
50–59	0·52 (0·47–0·58)	<0·0001
60–69	1 (ref)	
70–79	1·94 (1·81–2·08)	<0·0001
≥80	4·52 (4·23–4·84)	<0·0001
Index of multiple deprivation quintile		
1 (most deprived)	1·46 (1·37–1·56)	<0·0001
2	1·28 (1·20–1·37)	<0·0001
3	1·08 (1·01–1·16)	0·029
4	1·01 (0·94–1·08)	0·78
5 (least deprived)	1 (ref)	
Ethnicity		
Asian	1·08 (1·01–1·15)	0·021
Black	1·63 (1·51–1·77)	<0·0001
Mixed	1·30 (1·10–1·55)	0·0027
Other*	1·01 (0·86–1·18)	0·91
White	1 (ref)	
HbA_{1c}, mmol/mol		
<48	1·11 (1·05–1·18)	0·0005
48–53	1 (ref)	
54–58	1·05 (0·97–1·13)	0·23
59–74	1·22 (1·15–1·30)	<0·0001
75–85	1·36 (1·24–1·50)	<0·0001
≥86	1·61 (1·47–1·77)	<0·0001
eGFR, mL/min per 1·73 m^2		
≥90	1 (ref)	
60–89	1·02 (0·96–1·08)	0·51
45–59	1·39 (1·30–1·49)	<0·0001
30–44	1·76 (1·63–1·89)	<0·0001
15–29	2·31 (2·10–2·54)	<0·0001
<15	4·91 (4·34–5·56)	<0·0001
BMI, kg/m^2		
<20·0	2·33 (2·11–2·56)	<0·0001
20·0–24·9	1·34 (1·27–1·42)	<0·0001
25·0–29·9	1 (ref)	
30·0–34·9	1·04 (0·98–1·10)	0·23
35·0–39·9	1·17 (1·08–1·26)	<0·0001
≥40·0	1·60 (1·47–1·75)	<0·0001
Systolic blood pressure, mm Hg		
≤140	1 (ref)	
>140	0·86 (0·82–0·90)	<0·0001
Antihypertensive drugs		
No	1 (ref)	
Yes	1·09 (1·02–1·16)	0·014
Total cholesterol, mmol/L		
≤5	1 (ref)	
>5	1·03 (0·97–1·09)	0·42
Statins		
No	1 (ref)	
Yes	0·72 (0·69–0·75)	<0·0001
Tobacco smoking status		
Current smoker	0·67 (0·62–0·74)	<0·0001
Ex-smoker	1·13 (1·08–1·18)	<0·0001
Never smoked	1 (ref)	
Cardiovascular comorbidities		
Previous myocardial infarction	1·11 (1·00–1·23)	0·041
Previous stroke	2·02 (1·88–2·17)	<0·0001
Previous heart failure	2·09 (1·99–2·21)	<0·0001

0·10 1·00 10·00



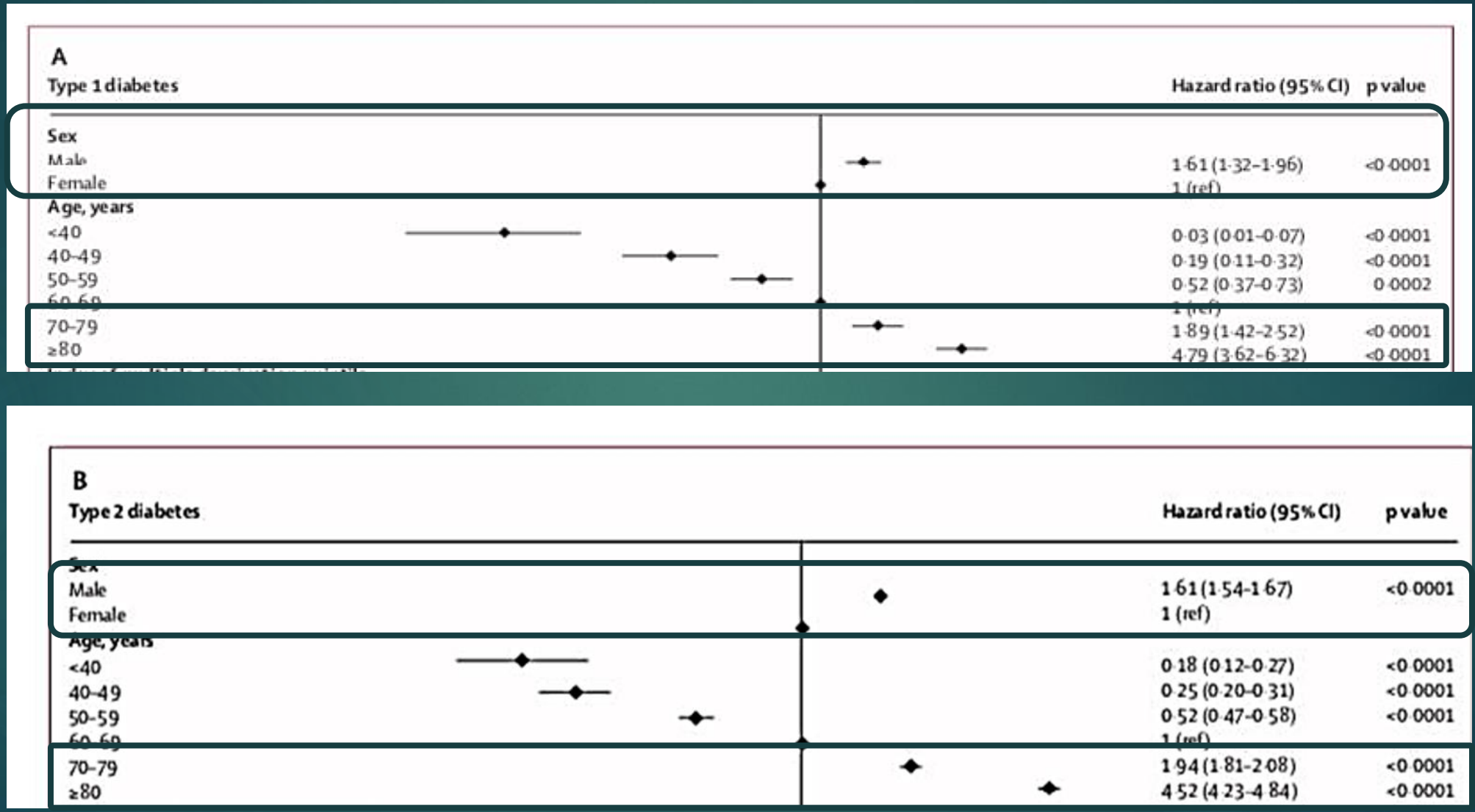
A Type 1 diabetes	Hazard ratio (95% CI)	p value
Sex		
Male	1·61 (1·32–1·96)	<0·0001
Female	1 (ref)	
Age, years		
<40	0·03 (0·01–0·07)	<0·0001
40–49	0·19 (0·11–0·32)	<0·0001
50–59	0·52 (0·37–0·73)	0·0002
60–69	1 (ref)	
70–79	1·89 (1·42–2·52)	<0·0001
≥80	4·79 (3·62–6·32)	<0·0001
Index of multiple deprivation quintile		
1 (most deprived)	1·93 (1·36–2·72)	0·0002
2	1·59 (1·13–2·25)	0·0086
3	1·82 (1·30–2·56)	0·0005
4	1·22 (0·84–1·76)	0·30
5 (least deprived)	1 (ref)	
Ethnicity		
Asian	1·57 (1·16–2·12)	0·0034
Black	1·77 (1·25–2·49)	0·0012
Mixed	0·86 (0·32–2·33)	0·77
Other*	1·89 (1·03–3·47)	0·040
White	1 (ref)	
HbA_{1c}, mmol/mol		
<48	1·37 (0·89–2·09)	0·15
48–53	1 (ref)	
54–58	0·78 (0·48–1·25)	0·30
59–74	1·16 (0·81–1·67)	0·42
75–85	1·37 (0·90–2·07)	0·14
≥86	2·23 (1·50–3·30)	<0·0001
eGFR, mL/min per 1·73 m^2		
≥90	1 (ref)	
60–89	1·17 (0·87–1·57)	0·30
45–59	2·07 (1·48–2·89)	<0·0001
30–44	2·46 (1·72–3·52)	<0·0001
15–29	3·71 (2·47–5·58)	<0·0001
<15	8·35 (5·50–12·70)	<0·0001
BMI, kg/m^2		
<20·0	2·45 (1·60–3·75)	<0·0001
20·0–24·9	1·51 (1·15–1·98)	0·0027
25·0–29·9	1 (ref)	
30·0–34·9	1·47 (1·12–1·94)	0·0059
35·0–39·9	1·72 (1·21–2·46)	0·0028
≥40·0	2·33 (1·53–3·56)	<0·0001
Systolic blood pressure, mm Hg		
≤140	1 (ref)	
>140	0·85 (0·69–1·05)	0·13
Antihypertensive drugs		
No	1 (ref)	
Yes	1·10 (0·81–1·49)	0·54
Total cholesterol, mmol/L		
≤5	1 (ref)	
>5	1·10 (0·83–1·46)	0·50
Statins		
No	1 (ref)	
Yes	0·82 (0·65–1·03)	0·081
Tobacco smoking status		
Current smoker	0·88 (0·62–1·25)	0·48
Ex-smoker	1·09 (0·89–1·35)	0·39
Never smoked	1 (ref)	
Cardiovascular comorbidities		
Previous myocardial infarction	1·25 (0·85–1·84)	0·25
Previous stroke	2·33 (1·72–3·15)	<0·0001
Previous heart failure	1·80 (1·41–2·29)	<0·0001

0·01 0·10 1·00 10·00

(Figure 2 continues on next page)

Risk Factors for COVID-19-related Mortality in People with Type 1and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

Sex & age in covid patients with type 1&2 DM



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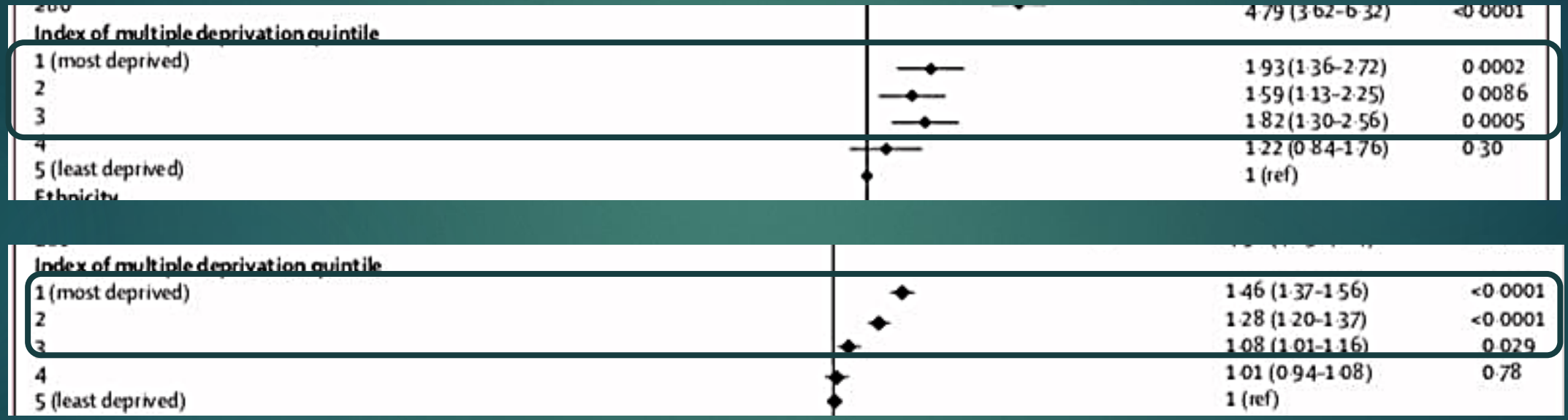
Socioeconomic deprivation in covid patients with type 1&2 DM



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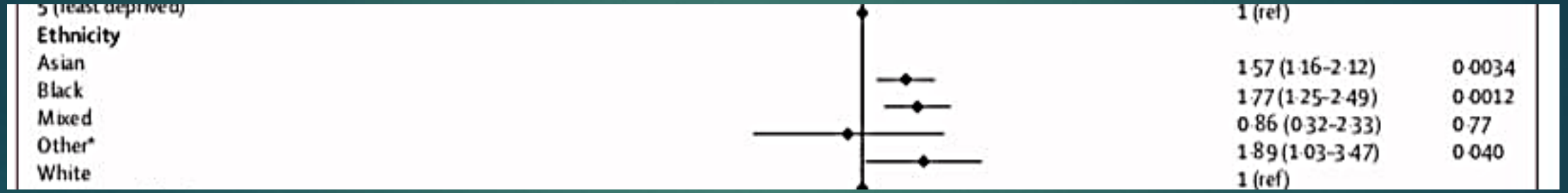
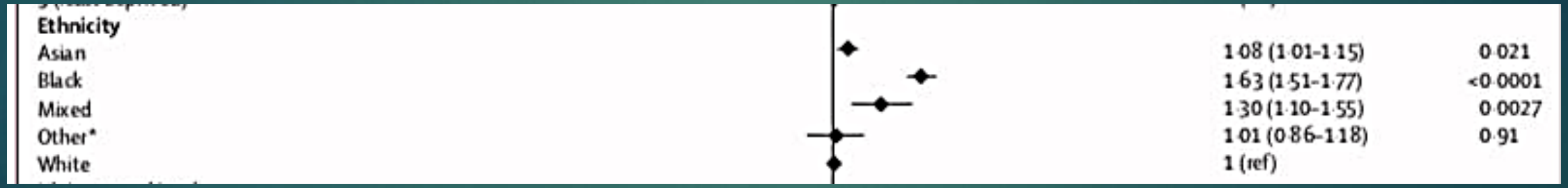
Ethnicity in covid patient with type 1&2 DM





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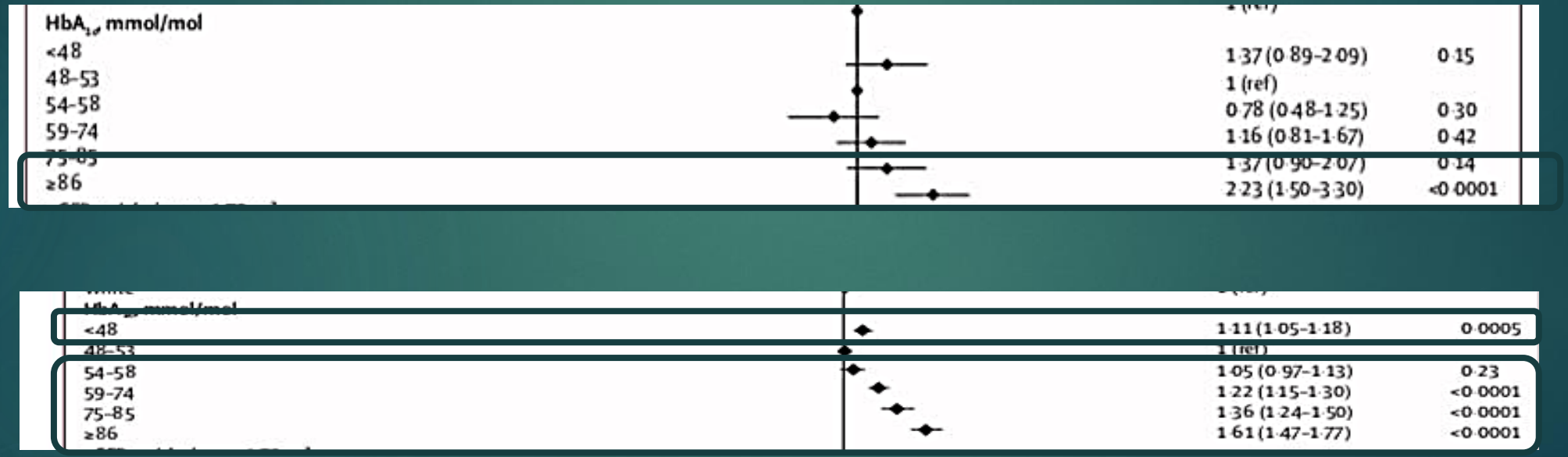
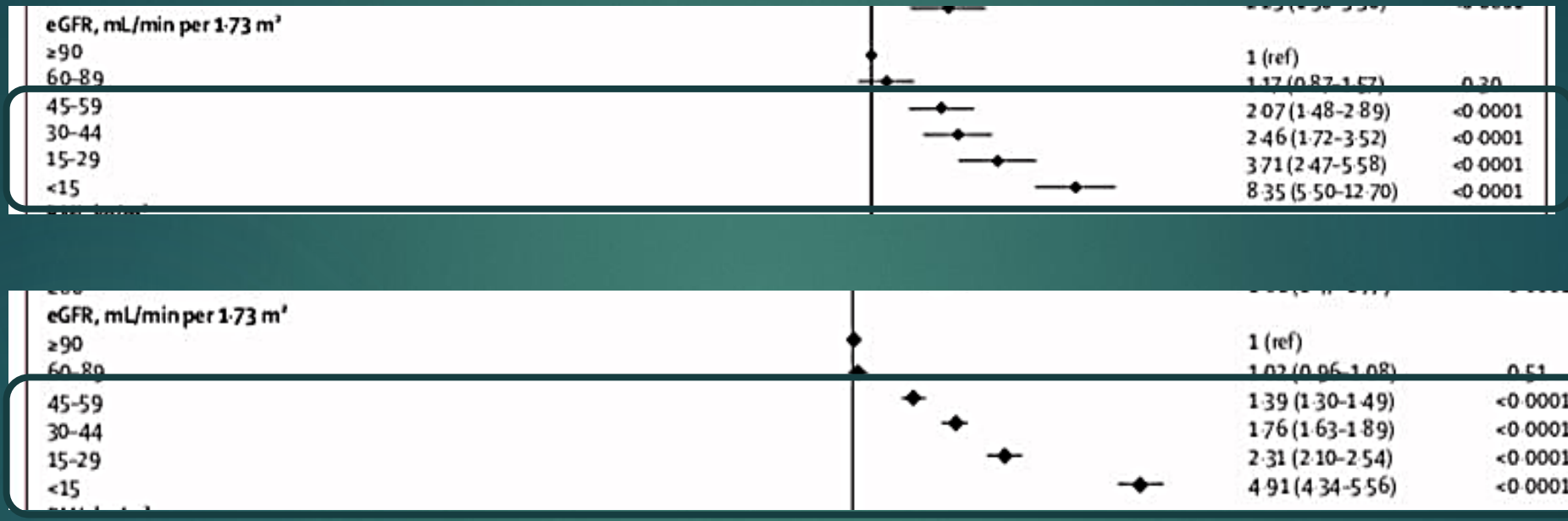
HBA1C in covid patients with type 1&2 DM



Risk Factors for COVID-19-related Mortality in People with Type 1 and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

GFR in covid patients with type 1&2 DM



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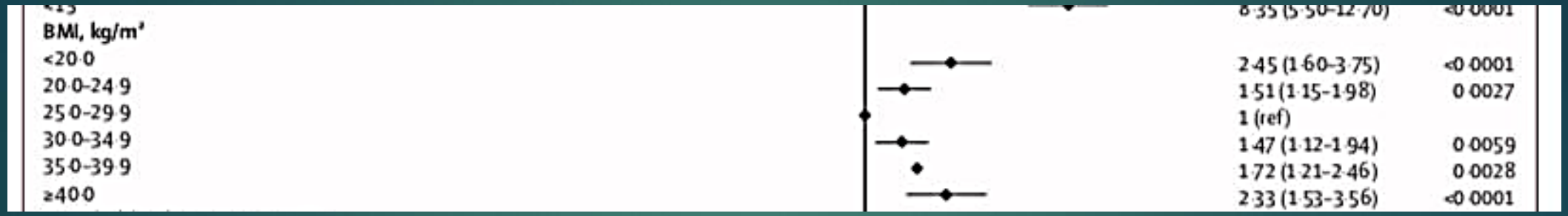
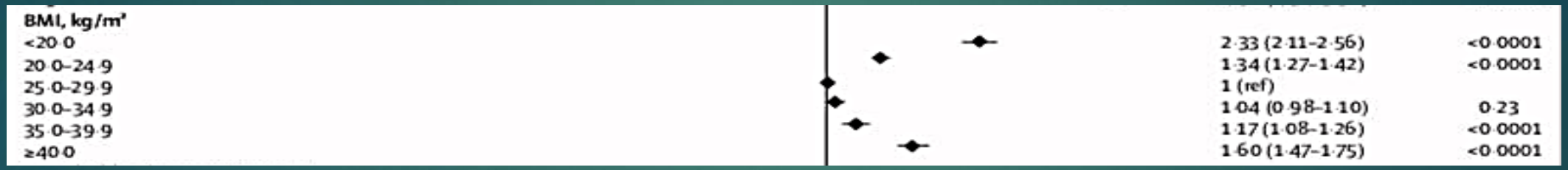
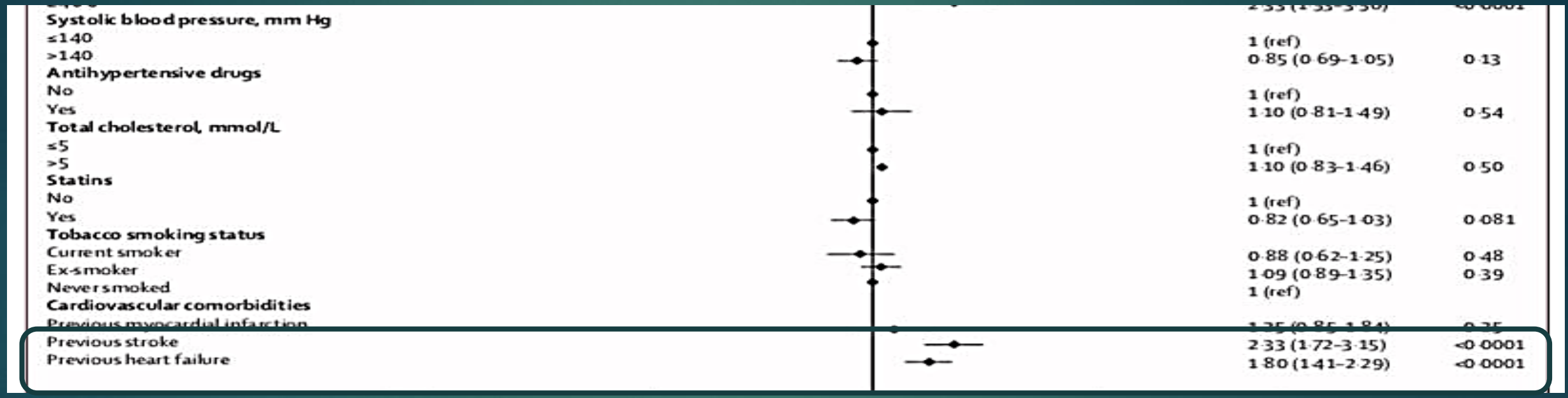
BMI in covid patients with type 1 &2 DM





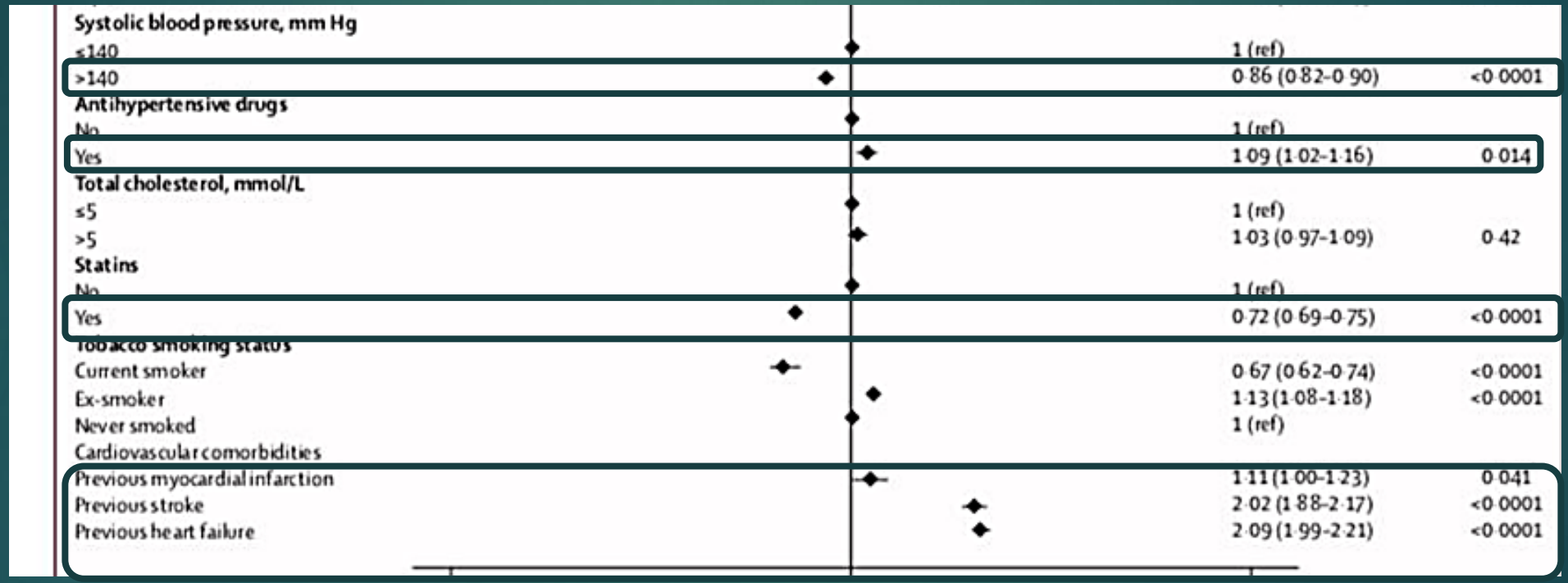
Risk Factors for COVID-19-related Mortality in People with Type 1and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

DM type 1



Risk Factors for COVID-19-related Mortality in People with Type 1and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

DM type 2



Risk Factors for COVID-19-related Mortality in People with Type 1 and Type 2 Diabetes in England: a Population-based Cohort Study . theLancet(2020)

Covid mortality risk factor in diabetic patients

Type 1

- Age>70 y/o
- Male sex
- Socioeconomic deprivation
- Non-white ethnicity
- HBA1C>10%
- GFR<60
- BMI<20 &>30
- Previous stroke/HF
- No benefit for statin

Type 2

- Age>70 y/o
- Male sex
- Socioeconomic deprivation
- Non-white ethnicity
- HBA1C>7.6% <6.5%
- GFR<60
- BMI<20 & >35
- SBP>140 protective
- Previous MI/stroke/HF
- Statin had benefit

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
- What are the cause of hyperglycemia in covid-19?
- How glycemic control can influence COVID mortality?
- What are the glycemic target in COVID patients?
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- How should GIH be managed?
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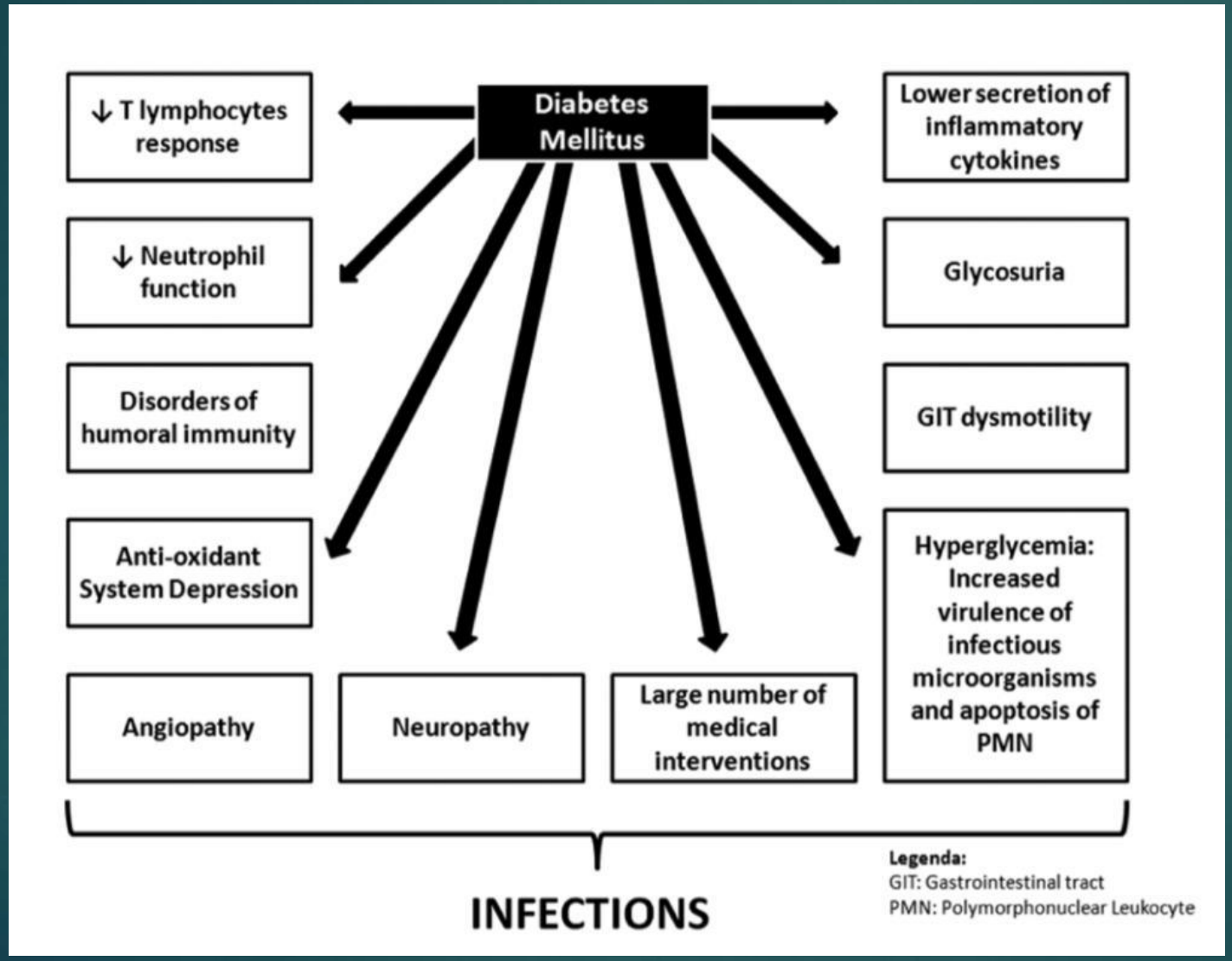
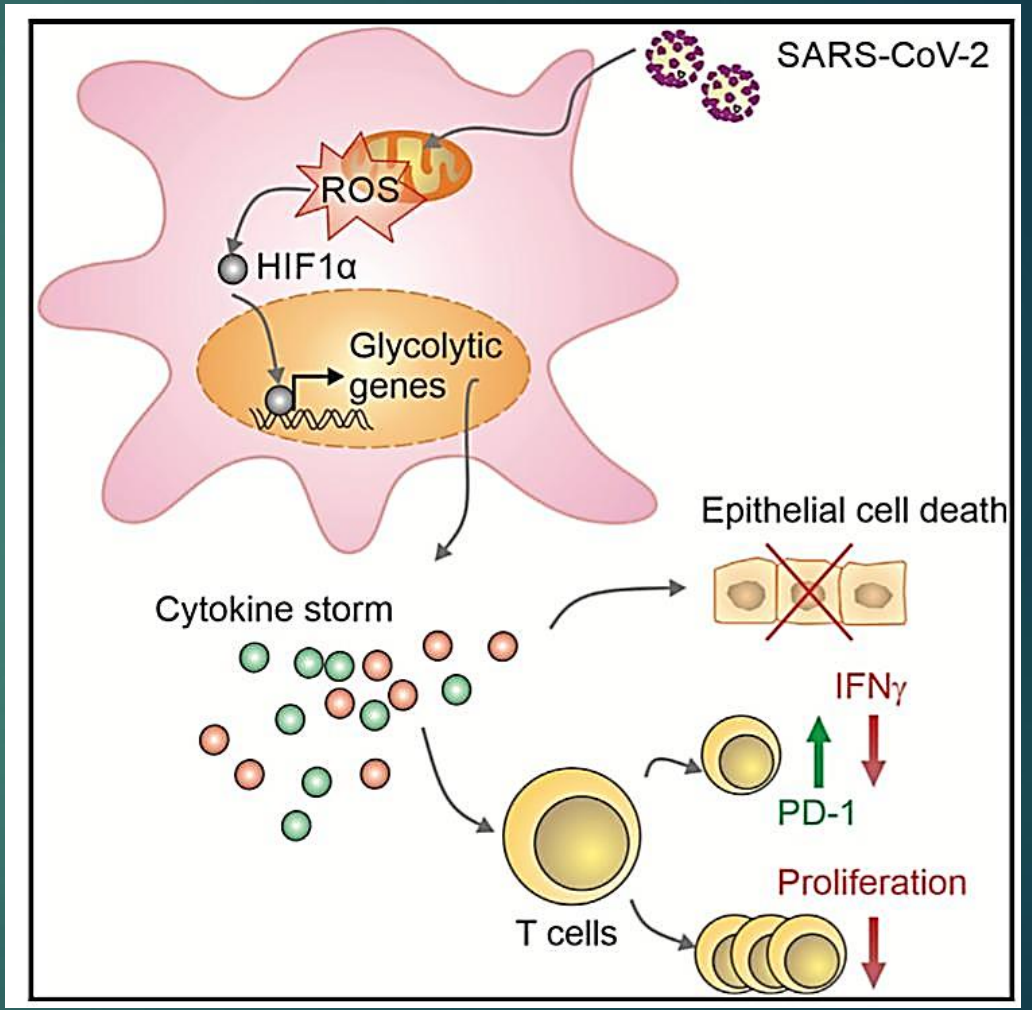
DM & defective immune system



Dm & immune response

- Elevated glucose level &glycolysis promote SARS-COV2 replication &cytokine production in monocytes .
- Resulting in T cell dysfunction & epithelial cell death.



DM & reduced NK activity

Table 2 | Correlation analysis between biochemical parameters including natural killer cell activity after adjusting for age, sex, blood pressure and smoking status

	NK cell activity							
	Type 2 DM		Prediabetes		NGT		All participants	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
BMI	0.193	0.459	0.409	0.240	−0.040	0.925	0.162	0.294
FPG	−0.705	<0.001	−0.208	0.565	−0.395	0.333	−0.745	<0.001
HbA1c	−0.790	<0.001	−0.470	0.170	−0.751	0.032	−0.827	<0.001
2hPG	−0.795	<0.001	0.268	0.453	−0.608	0.109	−0.778	<0.001
Total cholesterol	−0.264	0.306	0.032	0.929	−0.407	0.317	−0.245	0.109
Triglyceride	−0.003	0.990	0.624	0.054	−0.419	0.302	−0.183	0.235
HDL cholesterol	−0.131	0.616	−0.427	0.219	0.332	0.422	0.036	0.818
LDL cholesterol	−0.267	0.300	0.188	0.604	−0.448	0.265	−0.186	0.228
Fasting C-peptide	−0.350	0.169	0.179	0.621	0.196	0.642	0.219	0.153
Fasting insulin	−0.297	0.247	−0.009	0.980	0.749	0.032	0.302	0.046
HOMA-B	0.649	0.005	0.387	0.269	0.244	0.560	0.738	<0.001
HOMA-IR	−0.489	0.046	0.187	0.606	0.090	0.833	−0.212	0.166

Data are presented as the mean (standard deviation). 2hPG, 2-h postload glucose; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; LDL, low-density lipoprotein; NK, natural killer; NGT, normal glucose tolerance.

Relationship Between Natural Killer Cell Activity and Glucose Control in Patients with Type2 Diabetes and Prediabetes. J Diabetes Investig (2019)

questions

- Who are high risk patient for corona viruses?
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Causes of hyperglycemia in covid-19 patients

- Stress hyperglycemia
- Inflammation
- Autoimmune beta cell destruction(molecular mimicry)
- Pancreas direct damage by covid-19
- Drugs

Stress hyperglycemia:

- Hyperglycemia, insulin resistance, glucose intolerance
- Stress hyperglycemia associated with:
  - Mortality
  - Morbidity
  - Length of stay
  - Infection
  - Overall complication
- Attempts at intensive glycemic control, don't improve health care outcome

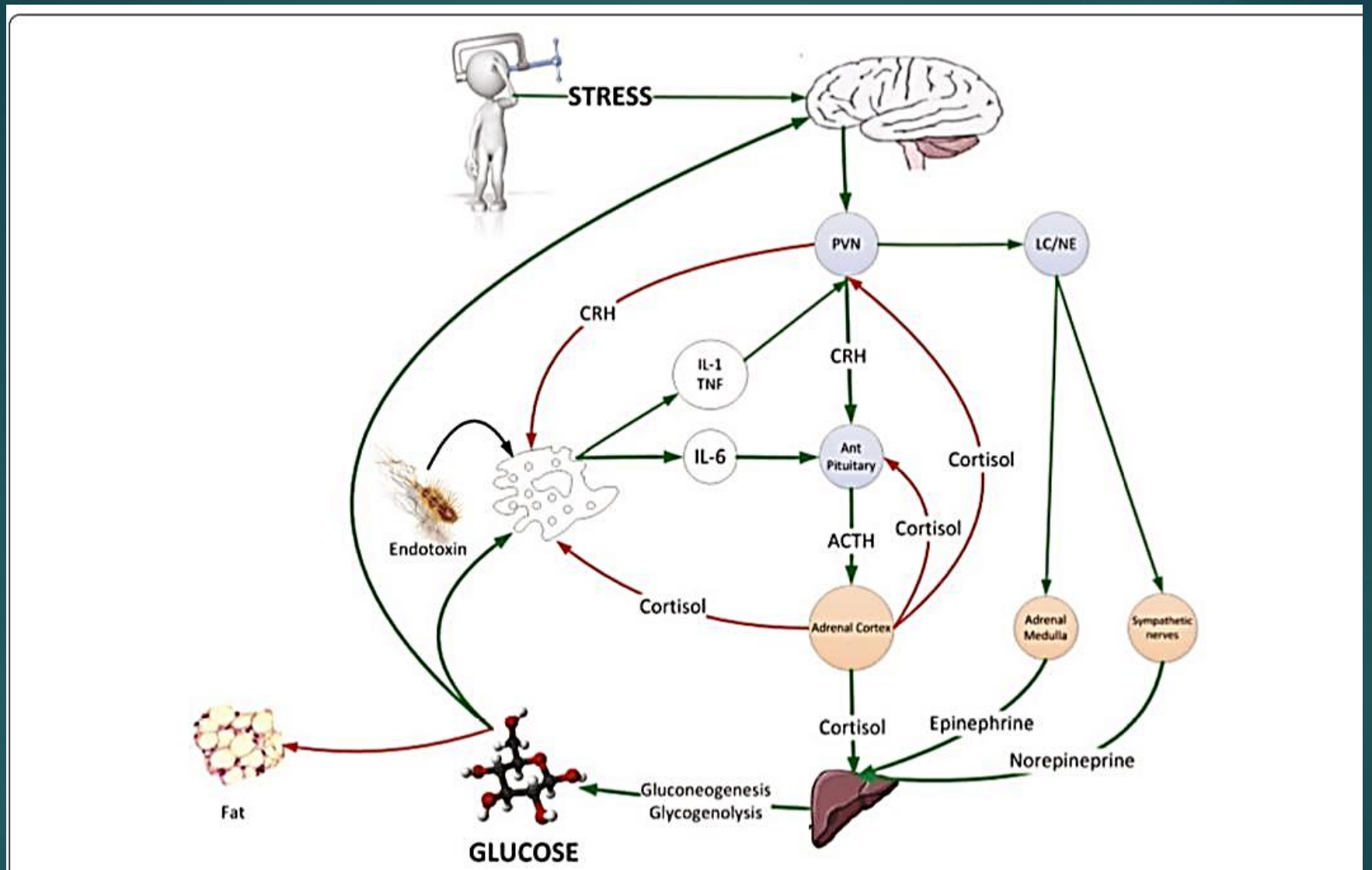


Figure 1. The neuroendocrine response to stress is characterized by gluconeogenesis and glycogenolysis resulting in stress hyperglycemia providing the immune system and brain with a ready source of fuel. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin releasing hormone; LC/NE, locus ceruleus norepinephrine system; PVN, paraventricular nucleus.

Stress hyperglycemia

- Degree of hyperglycemia associated with disease severity
- Hyperglycemia in acute illness setting is an adaptive response which increases host chance of survival.
- Patient with BS>220 benefit from moderate glycemic control.

Glycemic deterioration as a typical complication of COVID-19

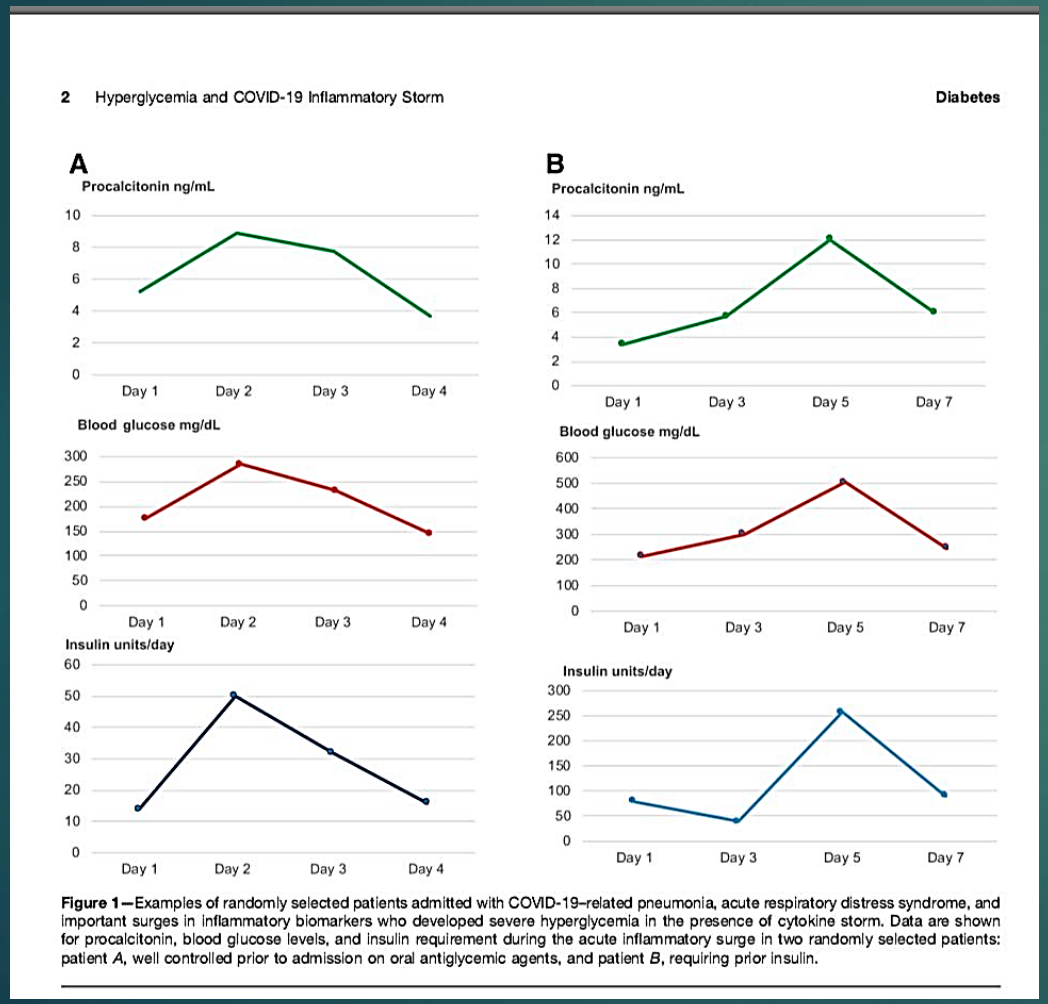


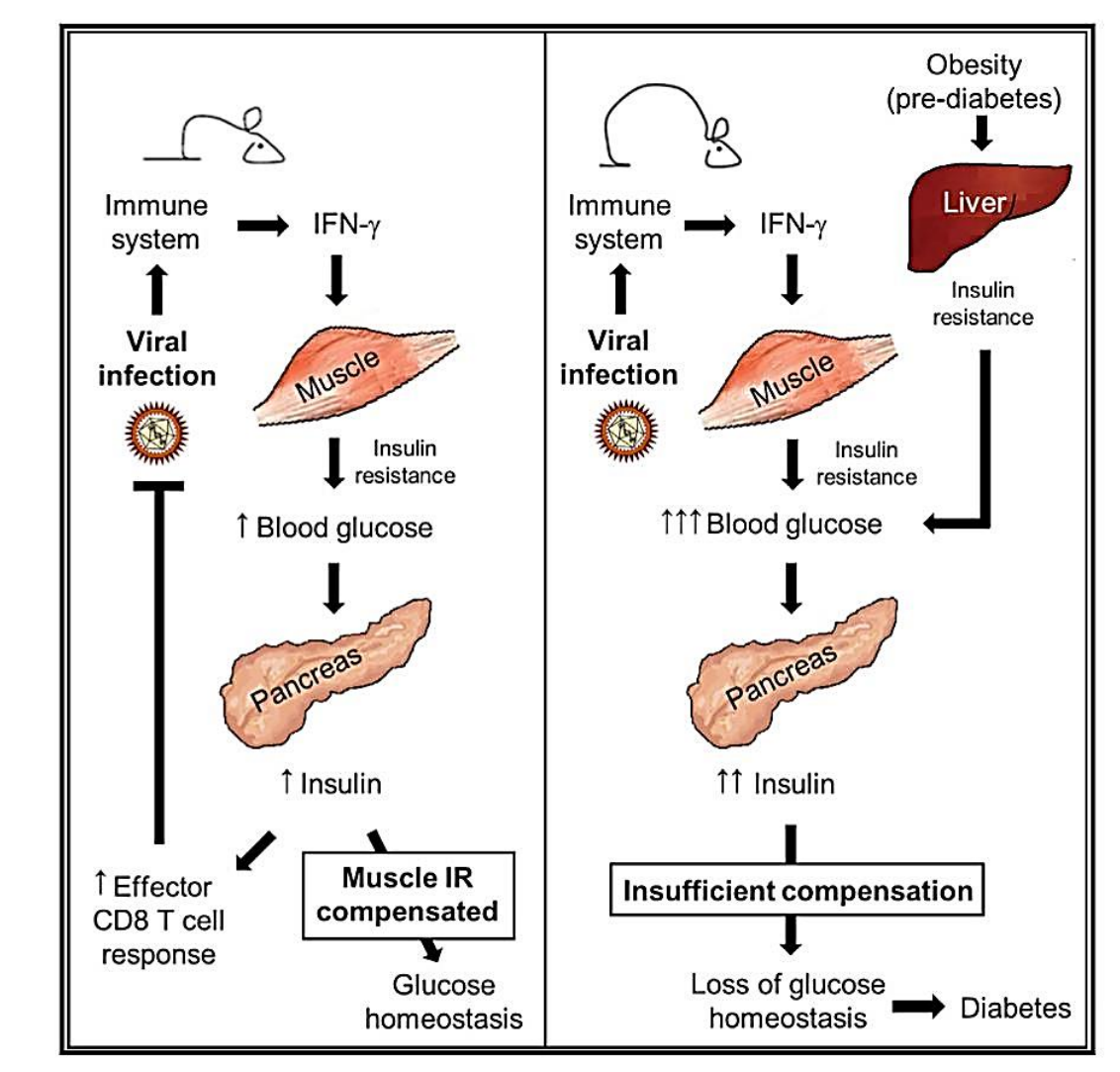
Figure 1—Examples of randomly selected patients admitted with COVID-19–related pneumonia, acute respiratory distress syndrome, and important surges in inflammatory biomarkers who developed severe hyperglycemia in the presence of cytokine storm. Data are shown for procalcitonin, blood glucose levels, and insulin requirement during the acute inflammatory surge in two randomly selected patients: patient *A*, well controlled prior to admission on oral antiglycemic agents, and patient *B*, requiring prior insulin.

FIGURE 1 Insulin requirements and inflammatory markers depicted for the eight patients throughout the course of admission. Total daily dose (units) is depicted in blue, and CRP (mg/L) is depicted in red. Patients 2, 3 and 6 were newly diagnosed with diabetes [Colour figure can be viewed at wileyonlinelibrary.com]

Managing Hyperglycemia in the COVID-19 Inflammatory Storm . DIABETES volume 69,October 2020

Insulin resistance

- Viral induced INF-gamma down regulate insulin receptor in skeletal muscle.
- Compensated increased insulin production.
- Hyperinsulinemia : enhance antiviral immunity through direct stimulation of CD8 effector T cell function.



Virus -induced Interferon Causes Insulin Resistance in Skeletal Muscle and Derails Glycemic Control in Obesity. Immunity 49,164-177(2018)

SARS pancreatic damage & acute diabetes

- Infection with covid cause hyperglycemia in people without pre-existing DM
- Localization of ACE2 in endocrine pancreas
- ACE2 association of COVID & DM
- Hyperglycemia can persist after recovery , long term damage to pancreatic beta cell

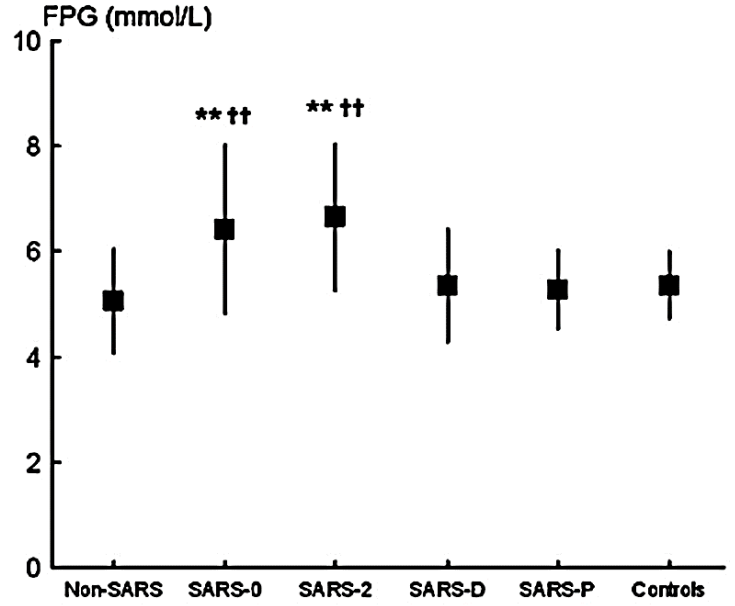


Fig. 3 Changes in FPG levels during the clinical course of SARS during follow-up. Non-SARS: FPG level in patients initially suspected of having SARS but later diagnosed with non-SARS pneumonia; SARS-0: the initial FPG level in SARS patients within 3 days after hospitalization; SARS-2: the initial FPG level after 2 weeks of hospitalization; SARS-D: the final FPG level before discharge; SARS-P: the FPG level from the follow-up study; Controls: the FPG level in the healthy siblings of SARS patients. $^{**}P < 0.01$ versus non-SARS patients. $^{\dagger\dagger}P < 0.01$ versus controls

Bindings of SARS Coronovirus to its Receptor Damages Islets and Causes Acute Diabetes .Acta Diabetol (2010)

Drugs for treating COVID & their glycemic effects:

Table 2 | **Glycaemic effects of potential pharmacological agents for COVID-19**

Drugs	Mechanisms of action	Source of data	Blood glucose	Insulin sensitivity or resistance	β-Cell function
Camostat mesylate	Serine protease (TMPRSS2) inhibitor	Human studies	↓ Patients with new-onset DM and chronic pancreatitis[172]	–	–
		Animal studies	↓ BG[175]; ↓ PPG[215]	↓ Insulin level[173]; ↓ insulin resistance[175]	↓ Insulin secretion (reversed by GIP)[216,217]
		Cells/organs	↓ BG[176]	↓ Insulin level[174]	–
		Patients with DM and/or insulin resistance	↓ BG[175]; ↓ PPG[215]	↓ Insulin level[173], ↓ insulin resistance[175]	–
Chloroquine or hydroxychloroquine	Blockade of virus entry and immunomodulation	Human studies	↓ HbA_{1c} (REFS[178,180,218]); ↓ FPG[178]; ↓ PPG or BG[180]; ↓ hazard ratio for incident new-onset DM by 38% in patients with RA[219]; hypoglycaemia[180,181]	↑ Insulin sensitivity[178]; ↑ hepatic insulin sensitivity[220]	↑ β-Cell function[178]
		Cells/organs	–	–	GLUT4 translocation and glucose uptake: ↓ in adipocytes[221], ↑ in muscle cells[222]
		Patients with DM and/or insulin resistance	↓ HbA_{1c} (REFS[178,180,218]); ↓ FPG[178]; ↓ PPG or BG[180]; ↓ hazard ratio for incident new-onset DM by 38% in patients with RA[219]; hypoglycaemia[180,181]	–	–

Kaletra

sofosbuvir

tocilizumab

anakinra

Protease inhibitors	Proteolytic processing of viral proteins	Human studies	↑ FPG[185]; ↑ BG[186,223]; ↑ in patients with new-onset DM[187]	↑ Insulin level[185,223,224]; ↓ insulin sensitivity[185,221,224]; ↓ glucose clearance[185]; ↓ non-oxidative glucose disposal[224,225]	↓ β-Cell function[185]; ↓ first-phase insulin release[185]
		Animal studies	–	–	↓ GLUT4 activity[226,227]
		Cells/organs	–	–	↓ GLUT4 activity[228] or mRNA[229]
RNA-dependent RNA polymerase inhibitors	Inhibition of RNA-dependent RNA polymerase	Animal studies	↓ FPG[191]	↓ Insulin level[191]; ↓ insulin resistance[193]	–
		Patients with DM and/or insulin resistance	↓ FPG[191]	↓ Insulin level[191]; ↓ insulin resistance[193]	–
IL-6 receptor inhibitors	IL-6 antagonism, suppressing the production of inflammatory molecules	Human studies	↓ HbA_{1c} (REF.[230])	↓ Insulin level[194]; ↓ insulin-to-glucose ratio[194]; ↑ insulin sensitivity[194]; ↓ insulin resistance[194]	–
		Animal studies	↓ Glucose intolerance[231]	–	–
		Cells/organs	–	–	↓ Transplanted islet cell death[231]
		Patients with DM and/or insulin resistance	↓ HbA_{1c} (REF.[230]); ↓ glucose intolerance[231]	–	↓ Transplanted islet cell death[231]
IL-1 receptor inhibitors	IL-1 antagonism	Human studies	↓ HbA_{1c} (REFS[196,232]); ↓ FPG[232]; no effect on HbA_{1c} and BG in patients with recent-onset T1DM[198]	↑ C-peptide secretion[196]; ↑ proinsulin-to-insulin ratio[196]	–
		Animal studies	↓ Glucose intolerance[231]	–	–
		Cells/organs	–	–	↑ Insulin secretion in transplanted islets[231]; ↓ transplanted islet cell death[231]
		Patients with DM and/or insulin resistance	↓ HbA_{1c} (REF.[232]); ↓ FPG[232]; no effect on HbA_{1c} and BG in patients with recent-onset T1DM[198]	No effect on C-peptide secretion in patients with T1DM[198]	↑ Insulin secretion in transplanted islets[231]; ↓ transplanted islet cell death[231]

rinolacept

tofacitinib

ibrutinib

Golimumab certolizumab

Table 2 (cont.) | **Glycaemic effects of potential pharmacological agents for COVID-19**

Drugs	Mechanisms of action	Source of data	Blood glucose	Insulin sensitivity or resistance	β-Cell function
IL-1β inhibitors	IL-1β antagonism	Human studies	No effect on HbA_{1c} in patients with recent-onset T1DM[198]	No effect on C-peptide secretion in patients with recent-onset T1DM[198]	–
		Patients with DM and/or insulin resistance	No effect on HbA_{1c} in patients with recent-onset T1DM[198]	No effect on C-peptide secretion in patients with recent-onset T1DM[198]	–
JAK1 and JAK2 inhibitors	Suppressing JAK–STAT signalling, inhibition of clathrin-medicated endocytosis, immunosuppression	Animal studies	↓ Reversal of new-onset DM in NOD mice[200]	↓ Insulin level[233]	–
		Patients with DM and/or insulin resistance	↓ DM development[200]	↓ Insulin level[233]	–
BTK inhibitor	Immunomodulatory effect on macrophages, reducing the production of cytokines	Animal studies	↓ BG[201]	–	–
TNF inhibitors	TNF antagonism	Human studies	↓ FBG[205,234,235]; ↓ HbA_{1c} (REFS[230,235]); ↓ patients with new-onset DM and RA and psoriasis[236]	↓ Insulin resistance[205,235,237]; ↑ insulin sensitivity[205,237]	↑ β-Cell function[205]
		Patients with DM and/or insulin resistance	↓ FBG[205,234,235]; ↓ HbA_{1c} (REFS[230,235])	↓ Insulin resistance[205]; ↑ insulin sensitivity[205]	↑ β-Cell function[205]
Corticosteroids[206,238]	Anti-inflammatory effects	Human studies	↑ HbA_{1c}; ↑ BG (mainly PPG)	↑ Insulin resistance; ↓ insulin sensitivity	↓ Insulin production and secretion

BG, blood glucose; BTK, Bruton's tyrosine kinase; COVID-19, coronavirus disease 19; DM, diabetes mellitus; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLUT4, glucose transporter type 4; JAK, Janus kinase; NOD, non-obese diabetic; PPG, postprandial glucose; RA, rheumatoid arthritis; STAT, signal transducer and activator of transcription; T1DM, type 1 diabetes mellitus; TMPRSS2, transmembrane protease serine 2; TNF, tumour necrosis factor.

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
- What are the cause of hyperglycemia in covid-19?
- How glycemic control can influence COVID mortality?
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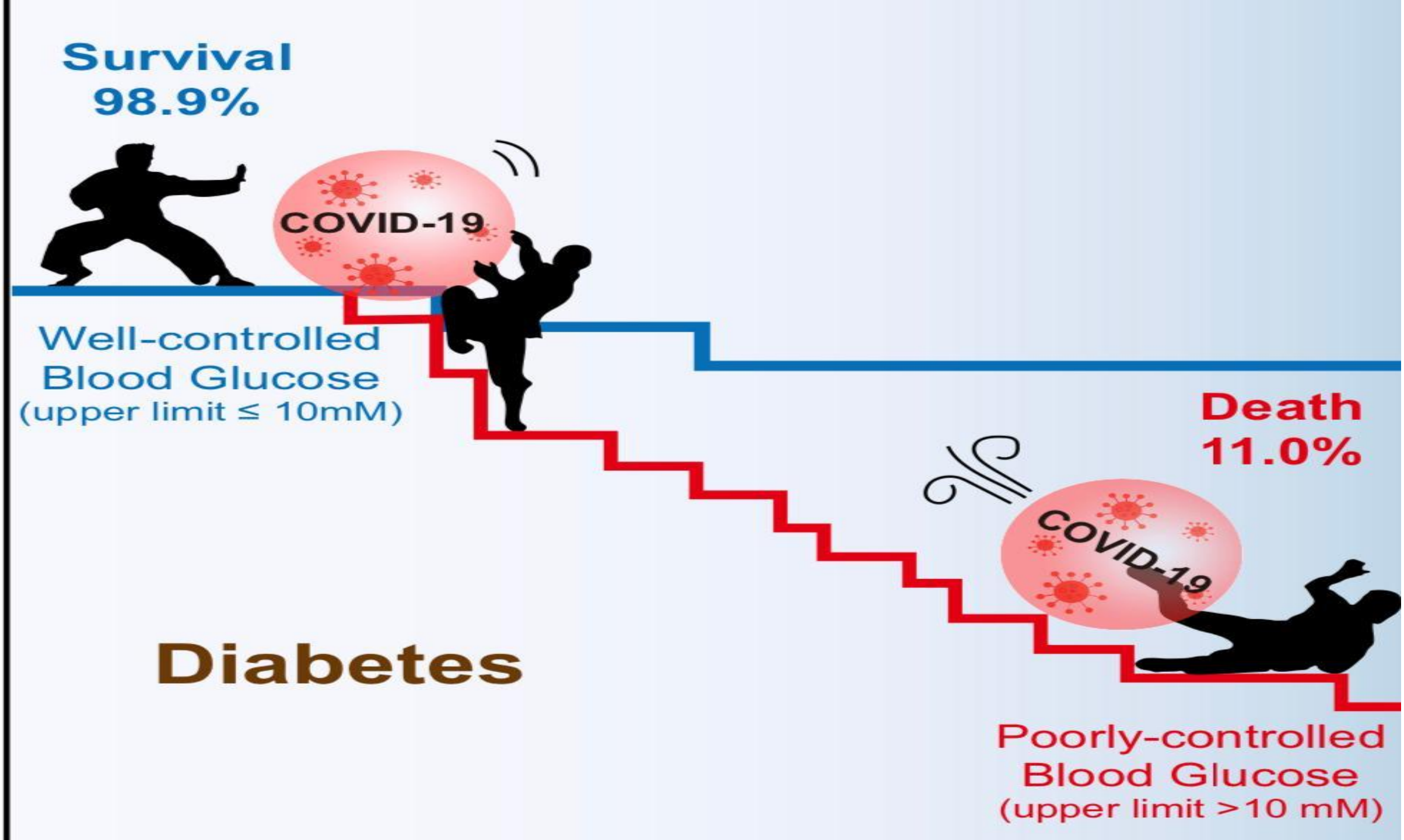
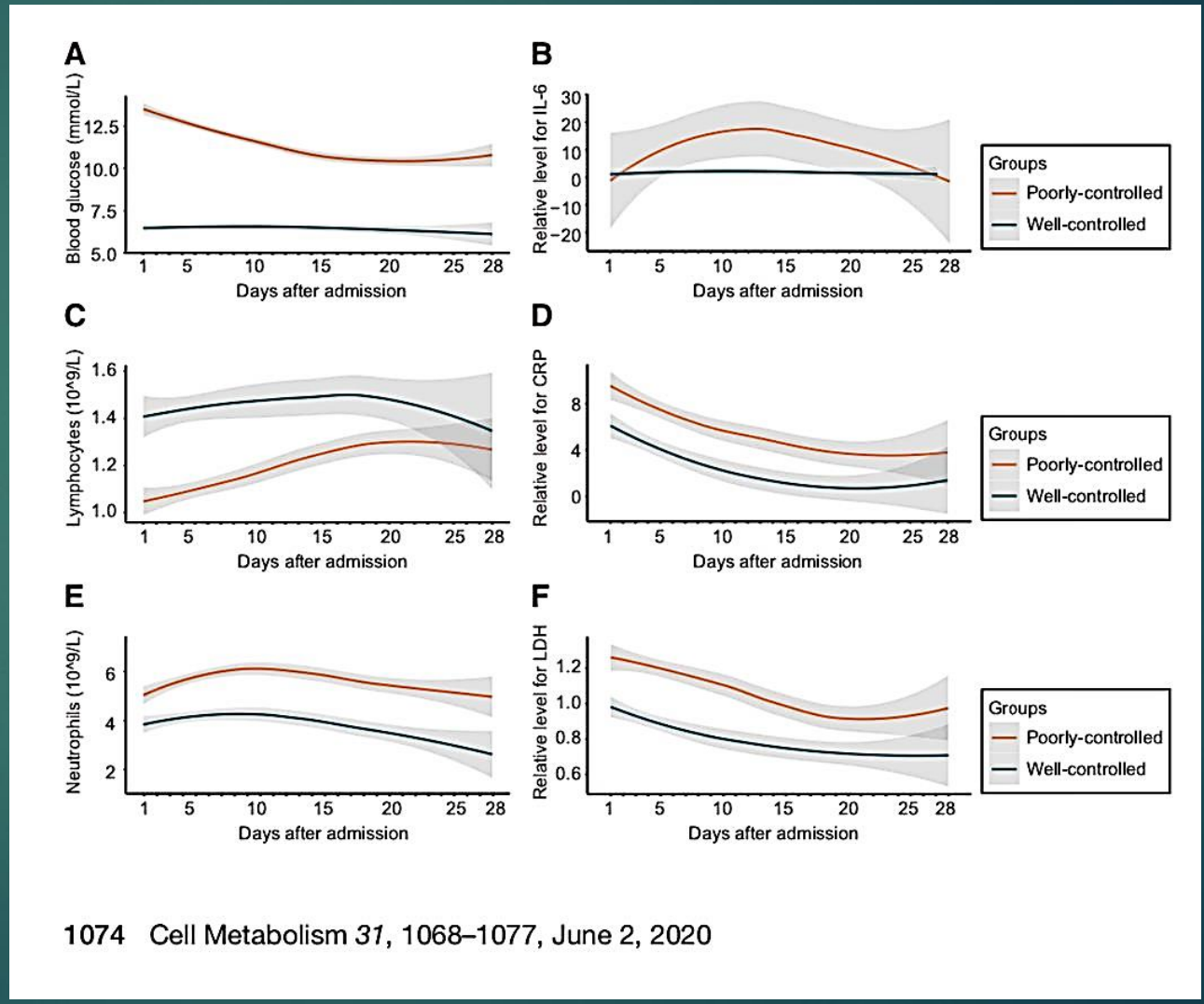

Survival
98.9%
COVID-19
Well-controlled
Blood Glucose
(upper limit ≤ 10mM)
Death
11.0%
COVID-19
Diabetes
Poorly-controlled
Blood Glucose
(upper limit >10 mM)

DM control & covid



1074 Cell Metabolism *31*, 1068–1077, June 2, 2020

Association of Blood Glucose Control and Outcome in Patients with COVID-19 and Pre-existing Type 2 Diabetes . Cell Metabolism(2020)

DM control & covid

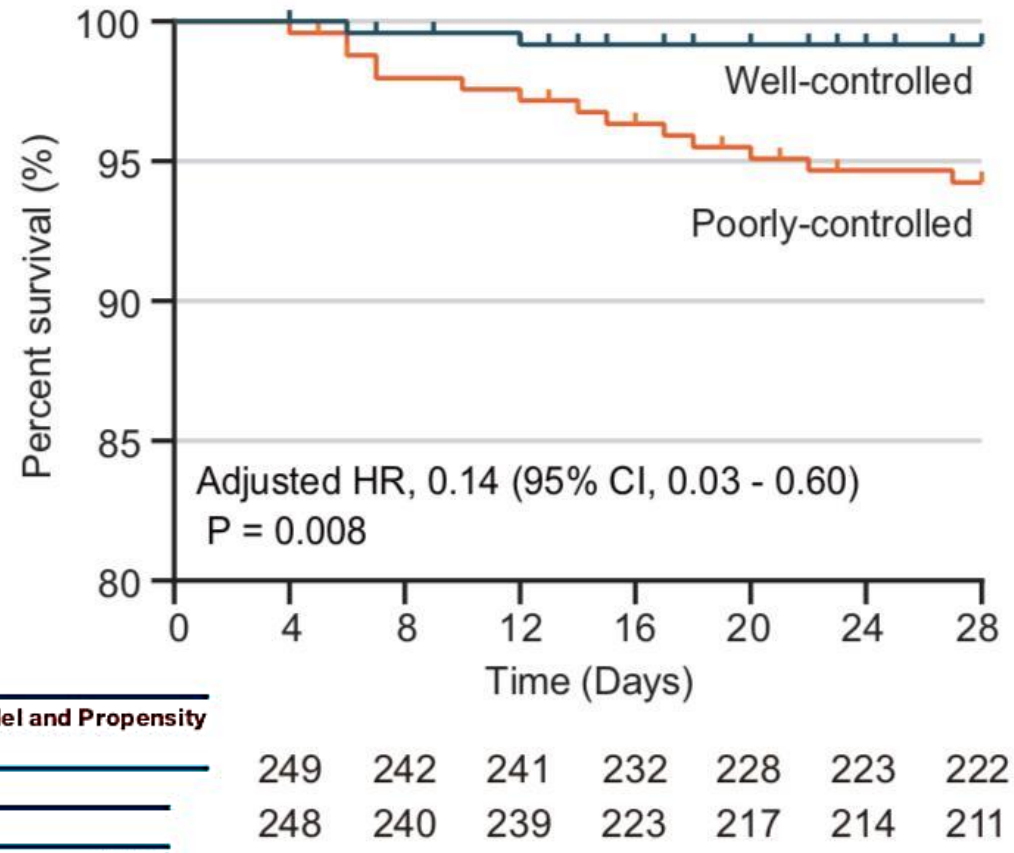
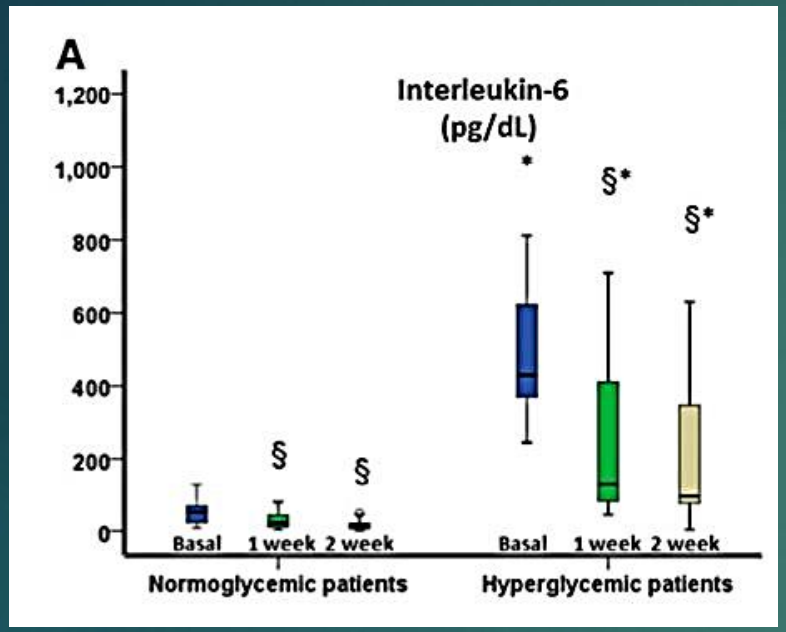


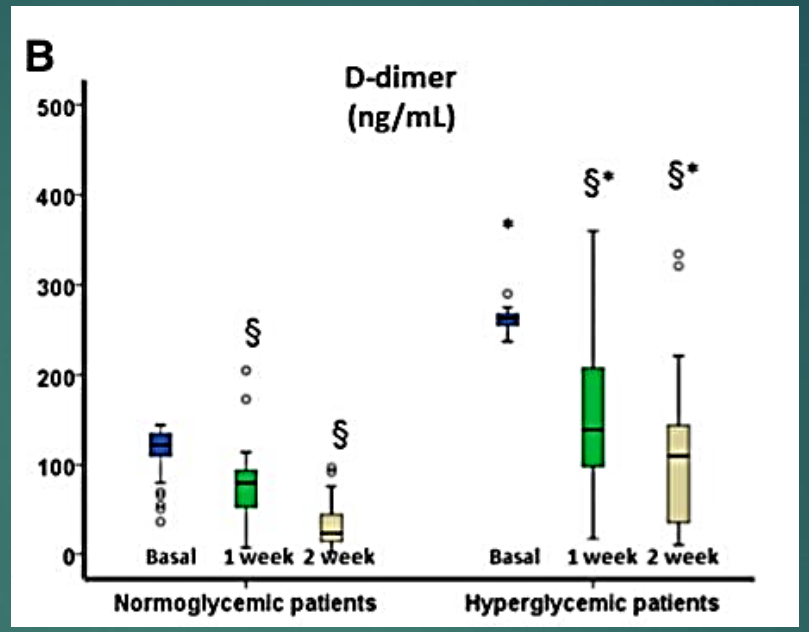
Table 3. Hazard Ratios for Outcomes in Well-Controlled and Poorly Controlled BG Cohorts under Cox Adjusted Model and Propensity Score-Matching Model

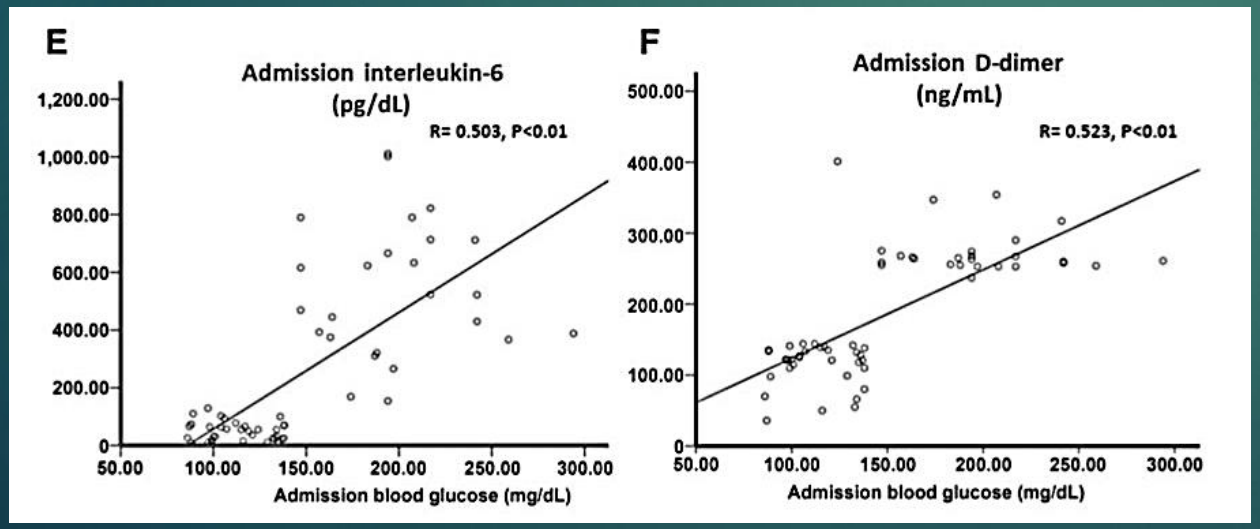
	Unmatched				Matched[b]	
	Crude		Adjusted[a]		Adjusted[c]	
Well-Controlled versus Poorly Controlled	HR (95% CI)	p Value[d]	HR (95% CI)	p Value[d]	HR (95% CI)	p Value[d]
All-cause mortality	0.09 (0.03,0.30)	<0.001	0.13 (0.04,0.44)	<0.001	0.14 (0.03,0.60)	0.008
Septic shock	–	–	–	–	–	–
ARDS	0.31 (0.19,0.50)	<0.001	0.41 (0.25,0.66)	<0.001	0.47 (0.27,0.83)	0.009
DIC	–	–	–	–	–	–
Acute kidney injury	0.19 (0.04,0.80)	0.024	0.22 (0.05,1.03)	0.055	0.12 (0.01,0.96)	0.046
Acute heart injury	0.14 (0.05,0.39)	<0.001	0.21 (0.07,0.59)	0.003	0.24 (0.08,0.71)	0.010

Association of Blood Glucose Control and Outcome in Patients with COVID-19 and Pre-existing Type 2 Diabetes . Cell Metabolism(2020)

hyperglycemia with or without DM & COVID

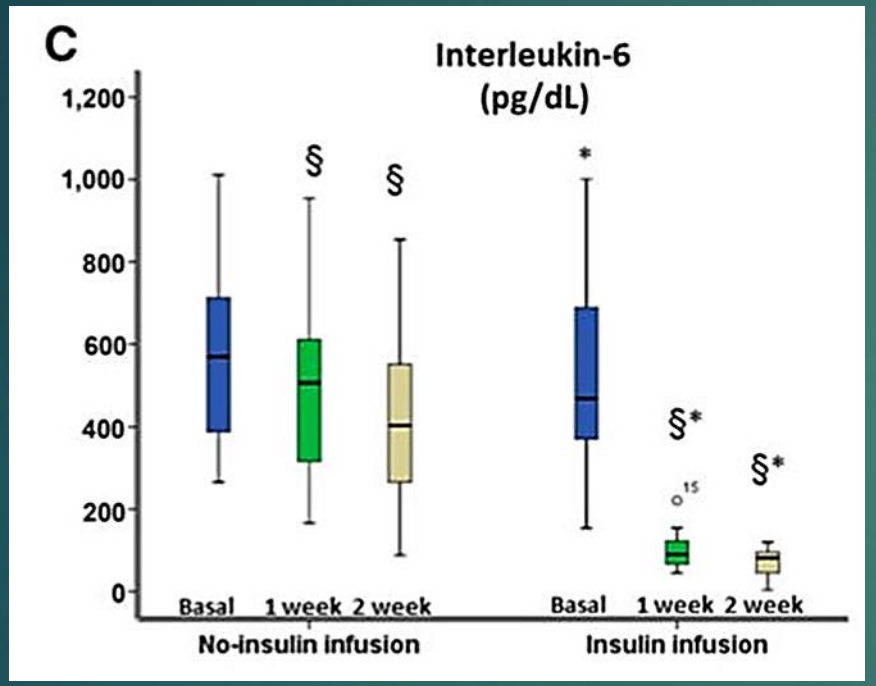


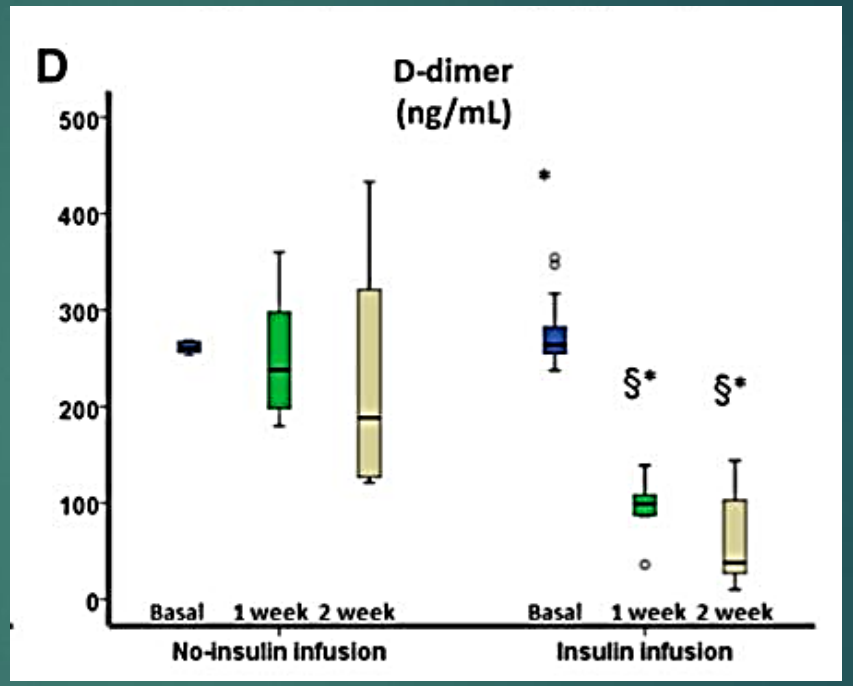




Outcomes in Patients with Hyperglycemia Affected by COVID-19:Can We Do More on Glycemic Control ? .Diabetes Care (2020)

Hyperglycemia control & covid-19





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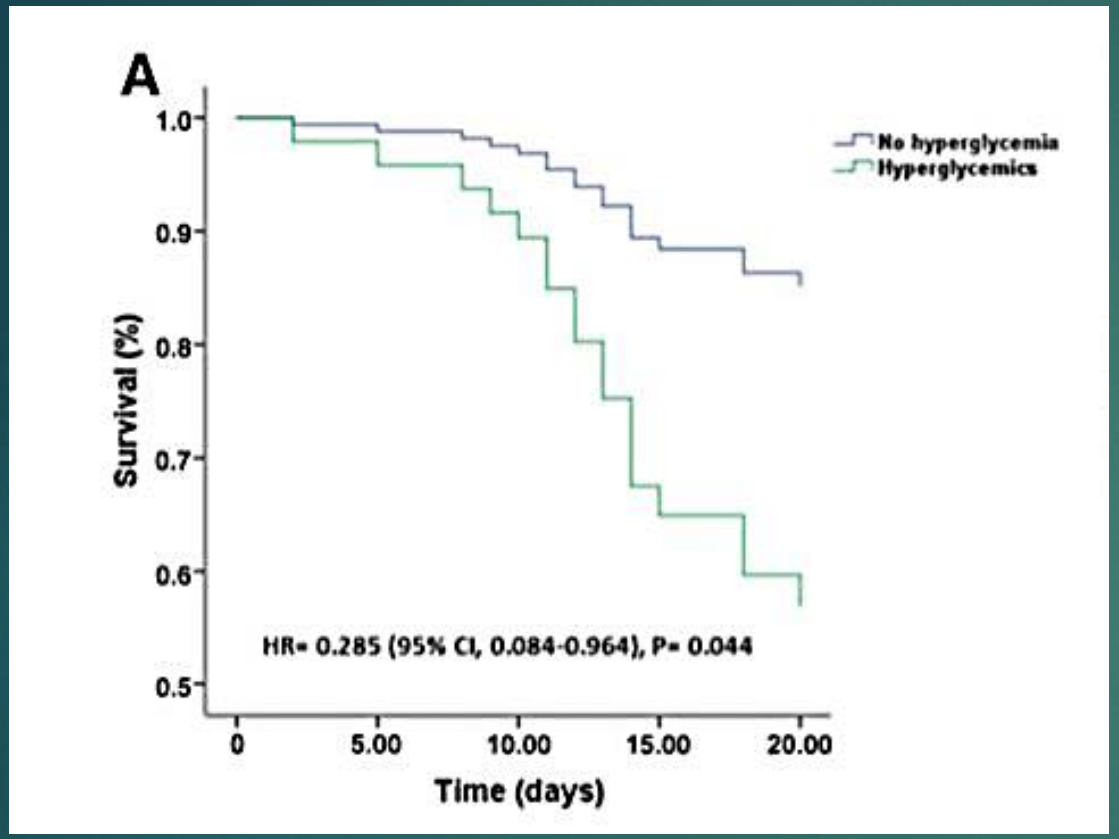

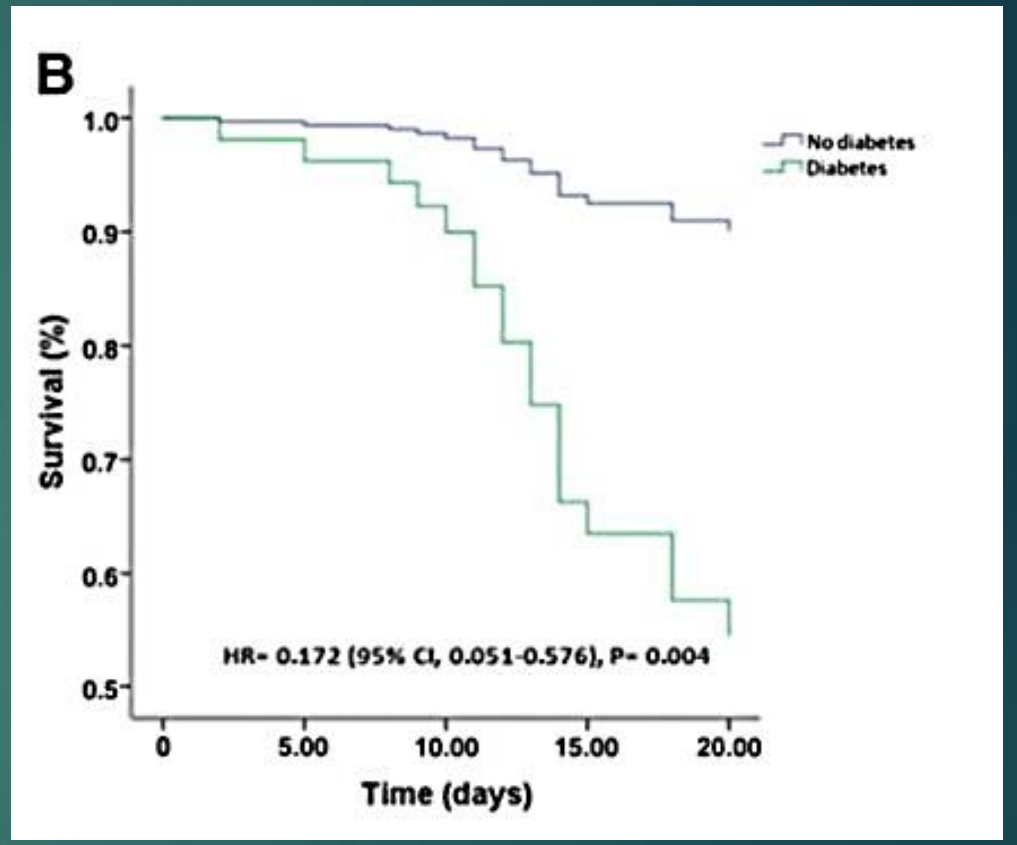

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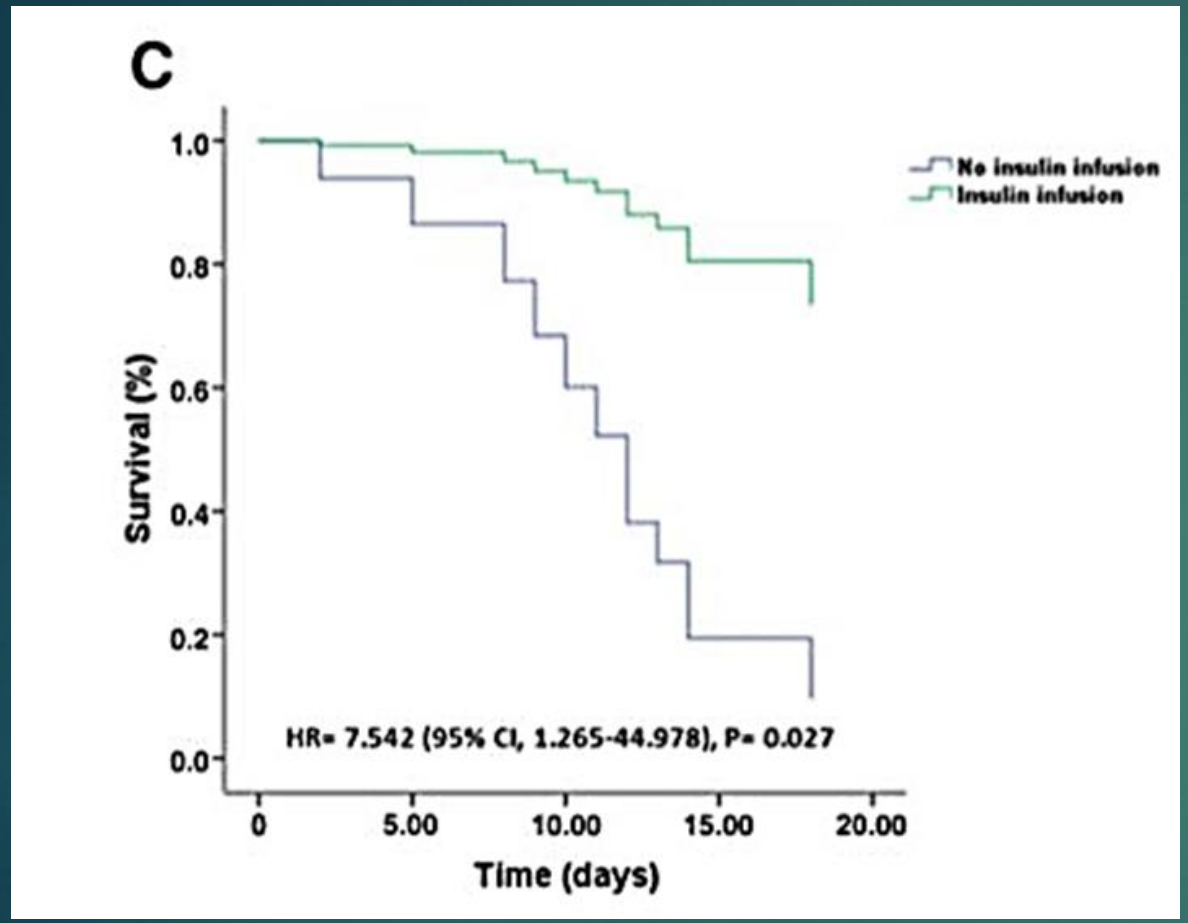

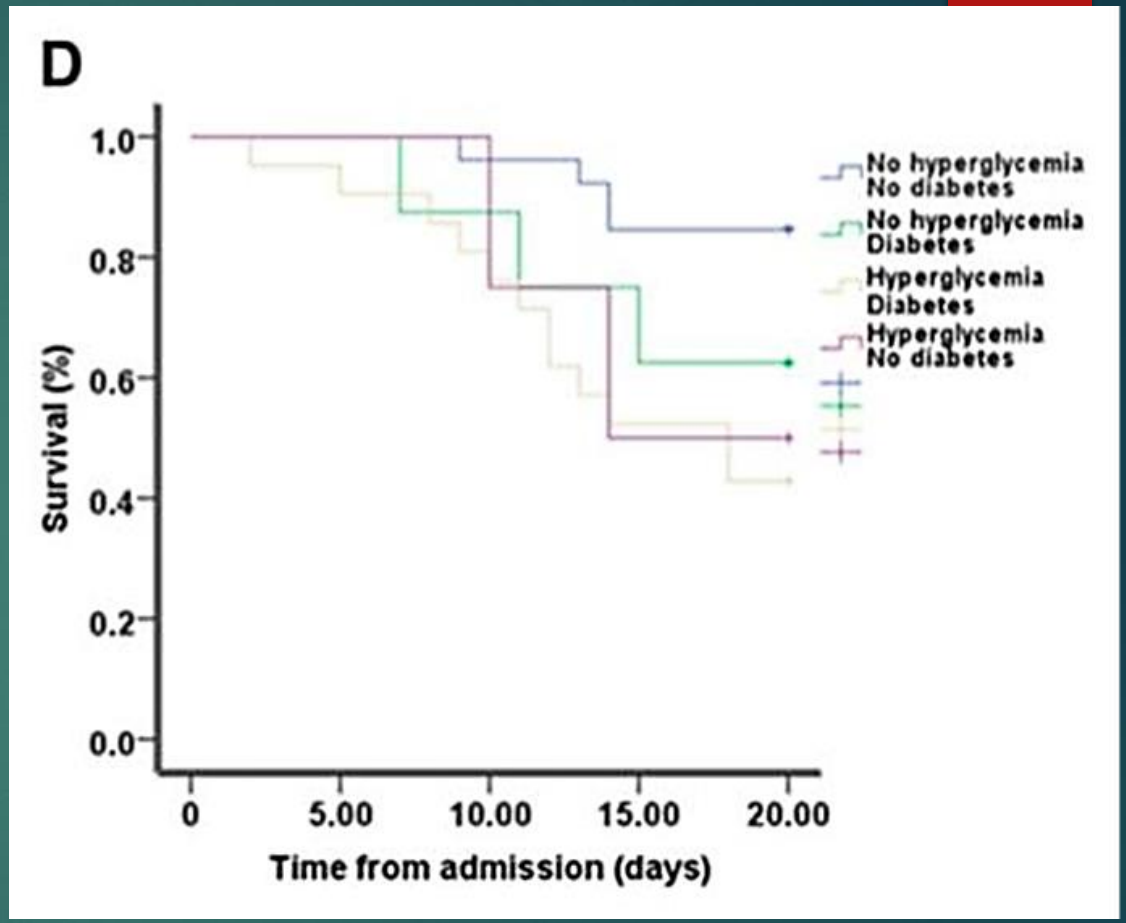

Outcomes in Patients with Hyperglycemia Affected by COVID-19:Can We Do More on Glycemic Control ? .Diabetes Care (2020)

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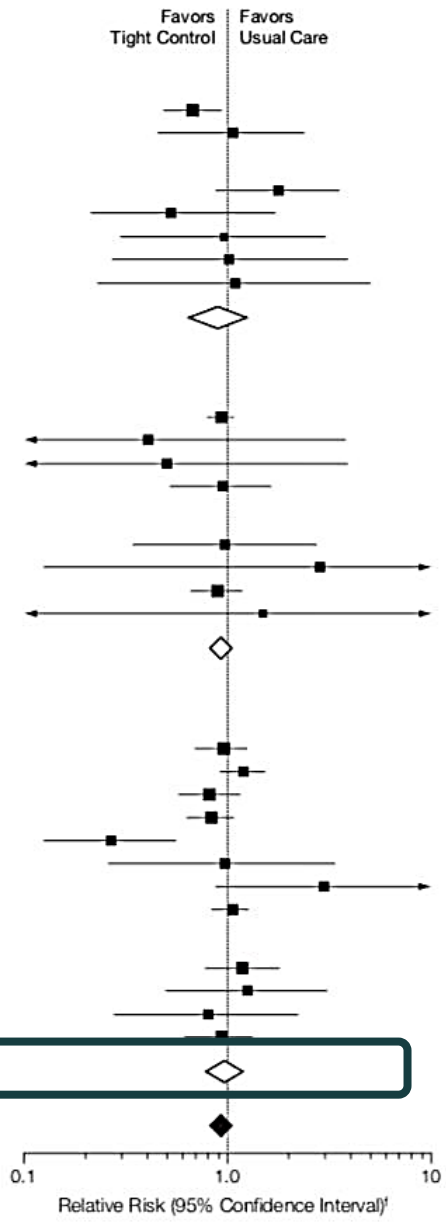
Figure 2. Association of Tight Glucose Control vs Usual Care With Hospital Mortality, Stratified by ICU Setting and Glucose Goal in Tight Control Group

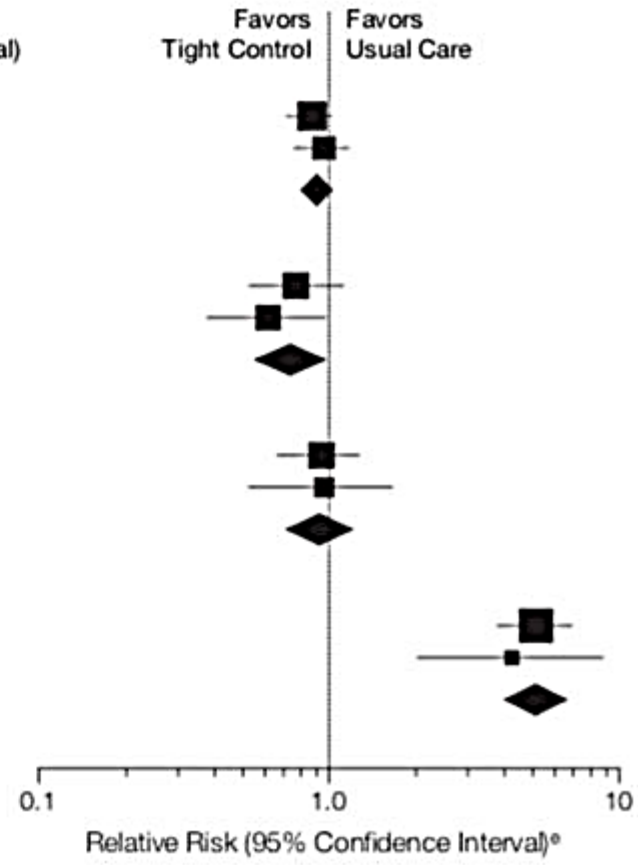
Source	Hospital Mortality, No./Total No. of Patients: Tight Control	Hospital Mortality, No./Total No. of Patients: Usual Care	Relative Risk (95% Confidence Interval)
Surgical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Van den Berghe et al,[1] 2001	55/765	85/783	0.66 (0.48-0.92)
Stecher et al,[27] 2006	9/57	9/60	1.05 (0.45-2.46)
Moderately tight control (glucose goal <150 mg/dL)			
Kia et al,[23] 2005	19/132	11/133	1.74 (0.86-3.51)
Grey and Perdrizet,[35] 2004	4/34	6/27	0.53 (0.17-1.69)
Bilotta et al,[36] 2007	5/40	5/38	0.95 (0.30-3.02)
Bilotta et al,[37] 2008	4/48	4/49	1.02 (0.27-3.85)
Chan et al, 2008[a]	3/47	3/51	1.09 (0.23-5.11)
All surgical ICU patients	99/1123	123/1141	0.88 (0.63-1.22)[b]
Medical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Van den Berghe et al,[15] 2006	222/595	242/605	0.93 (0.81-1.08)
Fernandez et al,[24] 2005	1/11	2/9	0.41 (0.04-3.82)
Bland et al,[38] 2005	1/5	2/5	0.50 (0.06-3.91)
Oksanen et al,[39] 2007	13/39	18/51	0.94 (0.53-1.68)
Moderately tight control (glucose goal <150 mg/dL)			
Davies et al,[41] 1991	6/35	6/34	0.97 (0.35-2.72)
Walters et al,[43] 2006	1/13	0/12	2.79 (0.12-62.48)
Gray/GIST-UK et al,[44] 2007	76/464	86/469	0.89 (0.67-1.18)
Bruno/THIS et al,[45] 2008	1/31	0/15	1.50 (0.06-34.79)
All medical ICU patients	321/1193	356/1200	0.92 (0.82-1.04)[c]
Medical-surgical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Brunkhorst/VISEP et al,[16] 2008	61/247	75/289	0.95 (0.71-1.27)
Devos/GLUCONTROL et al,[17] 2007	107/550	89/551	1.20 (0.93-1.55)
Mackenzie/GLYCOGENIC et al,[25] 2005	39/121	47/119	0.82 (0.58-1.15)
Arabi et al,[26] 2006	72/266	83/257	0.84 (0.64-1.09)
Wang et al,[29] 2006	7/58	26/58	0.27 (0.13-0.57)
Yu et al,[30] 2005	4/28	4/27	0.96 (0.27-3.47)
Mitchell et al,[46] 2006	9/35	3/35	3.00 (0.89-10.16)
De La Rosa et al,[47] 2006	102/254	96/250	1.05 (0.84-1.30)
Moderately tight control (glucose goal <150 mg/dL)			
Farah et al,[48] 2007	22/41	22/48	1.17 (0.77-1.78)
McMullin/LOGIC et al,[49] 2007	6/11	4/9	1.23 (0.49-3.04)
Henderson/SUGAR et al,[50] 2005	5/32	7/35	0.78 (0.28-2.22)
Azevedo et al, 2008[a]	28/168	42/169	0.91 (0.62-1.34)
All medical-surgical ICU patients	472/1811	498/1847	0.95 (0.80-1.13)[d]
All critically ill patients	892/4127	977/4188	0.93 (0.85-1.03)[e]



Benefit and Risk of Tight Glucose Control in Critically Ill Adults. JAMA (2008)

Figure 3. Association of Tight Glucose Control vs Usual Care With Outcomes Among Critically Ill Adults, Stratified by Glucose Goal in Tight Control Group

Subgroup	No. of Studies	Outcome, No./Total No. of Patients (%)		Relative Risk (95% Confidence Interval)
		Tight Control	Usual Care	
Hospital mortality[a]				
Very tight control	14	702/3031 (23.2)	781/3099 (25.2)	0.90 (0.77-1.04)
Moderately tight control	13	190/1096 (17.3)	196/1089 (18.0)	0.99 (0.83-1.18)
Overall	27	892/4127 (21.6)	977/4188 (23.3)	0.93 (0.85-1.03)
Septicemia[b]				
Very tight control	4	186/1654 (11.2)	221/1672 (13.2)	0.80 (0.57-1.11)
Moderately tight control	5	26/295 (8.8)	43/295 (14.6)	0.64 (0.41-1.00)
Overall	9	212/1949 (10.9)	264/1967 (13.4)	0.76 (0.59-0.97)
New need for dialysis[c]				
Very tight control	5	172/1424 (12.1)	193/1475 (13.1)	0.95 (0.70-1.29)
Moderately tight control	4	28/366 (7.7)	29/364 (8.0)	0.98 (0.59-1.61)
Overall	9	200/1790 (11.2)	222/1839 (12.1)	0.96 (0.76-1.20)
Hypoglycemia (glucose ≤40 mg/dL)[d]				
Very tight control	11	409/2895 (14.1)	75/2952 (2.5)	5.23 (4.12-6.64)
Moderately tight control	4	41/380 (10.8)	9/386 (2.3)	4.37 (2.19-8.72)
Overall	15	450/3275 (13.7)	84/3338 (2.5)	5.13 (4.09-6.43)



Benefit and Risk of Tight Glucose Control in Critically Ill Adults.JAMA(2008)

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
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- How glycemic control can influence COVID mortality?
- What are the glycemic target in COVID patients?
- What are the effective treatments in out patients & hospitalized patients?
- How should GIH be managed?
- What is the prognosis of DKA in covid-19
- How should DKA be prevented/treated?

Covid patients who may not require scheduled insulin therapy

- Well controlled non-insulin treated type 2 diabetic patients
- Newly recognized hyperglycemia
- Check BS q6hr
- Correction insulin (100-180)
- Check HbA1c
- Continuing home diabetic medication may be considered
- If 24-36 hour BS<180 :check BS daily + correction insulin DC
- IF 24-36 hour BS>180 :scheduled insulin therapy should be initiated

Non insulin therapy in diabetic covid-19 patients

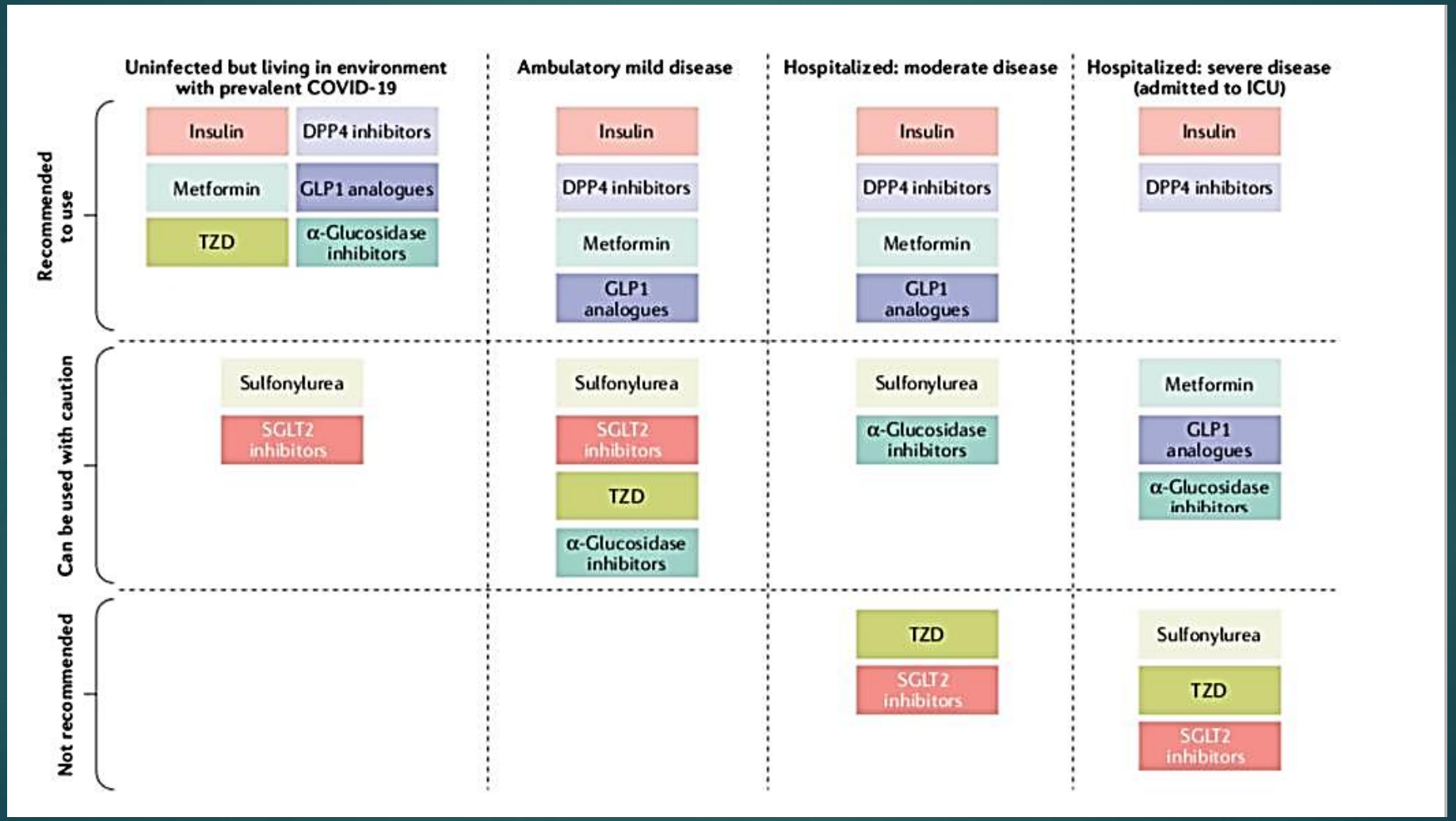
- Sulfonylureas, elevated hypoglycemia risk(AKI/elderly/insulin)
- Metformin CI in hypoxia/renal/hepatic dysfunction
- SGLT2 increase risk of DKA
- GLP1A risk of nausea/vomiting
- DPP4I: sitagliptin,linagliptin in selected patients:
  - Hospitalized patients with type 2 DM & mild hyperglycemia(BS<180 mg/dl)/in the recovery phase of covid-19
  - DPP4I +Insulin(correction/basal)
- TZD: late onset of action, fluid retention/HF aggregation

Table 1: Considerations for Non-Insulin Therapies in the Hospital Setting for COVID-19 Patients

Drug Class	Concerns for Hospital Use	Relevance to COVID-19 Patients
Sulfonylureas Insulin Secretagogues	High risk for hypoglycemia particularly in patients ≥ age 65, with eGFR ≤ 30 ml/min, or receiving insulin therapy	The occurrence of any hypoglycemic event increases need for interaction with hospital personnel.
Metformin	Contraindicated for patients with respiratory problems and hypoxia, hemodynamic instability, and unstable renal or hepatic function	Hospitalized patients with COVID-19 can experience sudden and rapid deteriorations in clinical status which contraindicates continued use of metformin in these patients when hospitalized
DPP 4 Inhibitors	DPP 4 enzyme has been identified as a co-receptor for the coronavirus which has potential to either favorably or unfavorably affect the binding of the virus to cell membranes. Majority of inpatient studies with these agents used these in combination with correction or basal insulin.	Generally not recommended in acute phase of COVID-19 due to concerns for abrupt deteriorations in clinical status. Saxagliptin and alogliptin should not be used as they are associated with higher risk for HF.
SGLT2 Inhibitors	Increases risk for euglycemic DKA, UTI, genital infections, and volume depletion	Discontinuation of these agents recommended at time of hospitalization.
GLP1 Receptor Agonists	Nausea and vomiting, particularly in patients who are not eating meals on a regular basis	Patients treated with long acting agents will have these on board at time of hospital admission. Continued use not currently recommended during acute hospitalizations.
Thiazolidinediones	Delay in glucose lowering effect, increase risk for fluid retention in insulin treated patients	These agents should not be used in this population.

A Pragmatic Approach to Inpatient Diabetes Management During the COVID-19 Pandemic. J Clin Endocrinol Metab.2020

Treatment option



Covid Patients who require insulin therapy

- Type1/type 2 insulin treated diabetes
- Type 2 diabetes with persistent BS>180
- Basal insulin (long acting)+prandial insulin for patients who are eating/ enteral / parenteral nutrition+ correction insulin for BS above target range
- Check BS :
  - PO patients: before each meal & bed time
  - NPO/enteral /parenteral nutrition :q4-6 hour

A Pragmatic Approach to Inpatient Diabetes Management During the COVID-19 Pandemic. J Clin Endocrinol Metab.2020

Table 2: Initiating Insulin Therapy in the Acute Care Setting*

	Basal Insulin	Prandial Insulin	Correction Insulin
Patients who are eating	Glargine U100 Starting dose: 0.1-0.2 units/kg/day**	Rapid acting analog 0.1 unit/kg/day in divided doses before meals	Administered prior to meals Reduce dose by 50% if given at bedtime
Patients who are NPO	Glargine U100 Dose: 0.1-0.2 units/kg/day	None	Administered every 4 to 6 hours as a rapid acting insulin analog or regular insulin, respectively
Patients receiving parenteral nutrition	Start if BG > 180 mg/dl despite use of insulin in TPN solution	1 unit/10 to 15 grams of carbohydrate in parenteral solution	Administered every 4 to 6 hours as a rapid acting insulin analog or regular insulin, respectively
Patients receiving continuous enteral nutrition±	NPH insulin administered every 8-12 hours with rapid acting or regular insulin administered every 4 to 6 hours Or Human 70/30 insulin administered every 8 to 12 hours Starting dose: 0.1-0.2 units/kg/day**		
	Alternative regimen: Glargine U100 Starting dose: 0.1-0.2 units/kg/day	Administer as rapid acting insulin analog or regular insulin every 4 to 6 hours according to duration of enteral nutrition¶	Administered as a rapid acting insulin analog or regular insulin every 4 to 6 hours, respectively
Patients receiving bolus enteral nutrition±	Administer rapid acting or regular insulin prior to administration of enteral nutrition (similar to patients eating meals). Some patients may also require basal insulin		Administered prior to bolus

A Pragmatic Approach to Inpatient Diabetes Management During the COVID-19 Pandemic. J Clin Endocrinol Metab.2020

Insulin infusion

- When glycemic control can not be achieved with SC insulin (alone/combination with basal insulin)
- Variation in insulin dose
- Insulin resistace,50 unit/hr insulin requirement/close monitoring >20unit/hr
- Basal insulin facilitate transition to SC
- When Stable infusion rate is achieved: check BS: q4-6

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Anti-inflammatory properties of antidiabetic drugs: A "promised land" in the COVID-19 era?

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[b] C.N.R. Institute of Clinical Physiology, Pisa, Italy

Table 1
Summary of the effects of antidiabetic drugs on C-reactive protein, interleukin-6 and ferritin in human studies.

	C-reactive protein	Interleukin-6	Ferritin
Metformin	↓ —	↓	↓
Pioglitazone	↓	—	No data
Sitagliptin	↓ —	↓ —	No data
Linagliptin	—	No data	—
Vildagliptin	↓ —	↓ —	No data
Alogliptin	—	↑	No data
Saxagliptin	—	—	No data
Liraglutide	↓ —	↓ —	↓
Dulaglutide	↓	↓	No data
Exenatide	↓	↓	No data
Lixisenatide	No data	No data	No data
Semaglutide	↓	No data	No data
Empagliflozin	↓ —	↓	↓
Dapagliflozin	↑↓ —	↓	↓
Canagliflozin	↓ —	↓ —	↓

Metformin & covid

Comparison of clinical outcome of patients between the metformin group and no-metformin group

Clinical outcome	Metformin group (n = 104)	No-metformin group (n = 179)	P-value
Hospitalization time (days)	21.0 (15.0–28.0)	19.5 (12.0–26.3)	0.74
In-hospital mortality, n (%)	3 (2.9%)	22 (12.3%)	0.01

Data are expressed as median (IQR) or number (%). P-values denoted the comparison between the metformin group and no-metformin group.

TABLE 1

Comparison of clinical characteristics of patients between the metformin group and no-metformin group

Characteristic	Metformin group (n = 104)	No-metformin group (n = 179)	P-value
Age (years)	63.0 (55.8–68.3)	65.0 (57.5–71.0)	0.06
Male gender, n (%)	53 (51.0)	103 (57.5)	0.28
Underlying disease, n (%)			
Hypertension	62 (59.6)	102 (57.0)	0.67
Coronary heart disease	11 (10.6)	32 (17.9)	0.10
Malignancies	1 (1.0)	6 (3.4)	0.40
Chronic nephrosis	1 (1.0)	3 (1.7)	1.00
Chronic obstructive pulmonary disease	0 (0.0)	6 (3.4)	0.09
Clinical severity, n (%)			0.40
Moderately ill	27 (26.0)	39 (21.8)	
Seriously ill	75 (72.1)	132 (73.7)	
Critically ill	2 (1.9)	8 (4.5)	
Oxygen-support category, n (%)			0.43
Ambient air	27 (26.0)	39 (21.8)	
Noninvasive oxygen support	76 (73.1)	135 (75.4)	
Invasive ventilation	1 (1.0)	5 (2.8)	

Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis.Am.J.Trop.Mee.Hyg,103(1),2020,pp.69-72

Metformin & covid

Comparison of laboratory value of patients between the metformin group and no-metformin group

Laboratory parameter	Metformin group (n = 104)	No-metformin group (n = 179)	P-value
White blood count ($\times 10^9$/L)	6.12 (5.12–7.20)	6.11 (5.02–7.98)	0.55
Lymphocyte count ($\times 10^9$/L)	1.24 (0.87–1.77)	1.08 (0.69–1.55)	0.13
Monocyte count ($\times 10^9$/L)	0.50 (0.41–0.63)	0.50 (0.36–0.64)	0.55
Neutrophil count ($\times 10^9$/L)	4.18 (3.29–5.19)	4.24 (3.09–5.87)	0.50
Eosinophil count ($\times 10^9$/L)	0.05 (0.01–0.11)	0.04 (0.00–0.09)	0.31
Basophil count ($\times 10^9$/L)	0.01 (0.01–0.03)	0.01 (0.01–0.02)	0.86
Platelet count ($\times 10^9$/L)	237 (177–314)	222 (160–274)	0.06
Alanine aminotransferase levels (U/L)	23.0 (14.5–32.5)	22.0 (15.0–33.5)	0.67
Aspartate aminotransferase levels (U/L)	23.5 (18.0–33.0)	25.0 (19.0–35.5)	0.39
Gamma-glutamyltransferase levels (U/L)	30.0 (20.0–46.3)	28.0 (19.0–50.0)	0.91
Serum creatinine levels (umol/L)	69.0 (57.0–85.0)	71.0 (56.0–90.0)	0.36
Blood urea levels (mmol/L)	4.95 (4.00–6.00)	5.10 (3.65–7.20)	0.38
C-reactive protein levels (mg/L)	20.7 (3.40–68.2)	20.9 (2.62–83.6)	0.78
Fasting blood glucose levels (mmol/L)	9.19 (6.83–14.8)	7.36 (6.10–11.8)	< 0.01

Data are expressed as median (IQR). P-values denoted the comparison between the metformin group and no-metformin group.

Comparison of treatment of patients between the metformin group and no-metformin group

Treatment	Metformin group (n = 104)	No-metformin group (n = 179)	P-value
Antidiabetic treatment, n (%)			
Insulins	61 (58.7%)	91 (50.8%)	0.20
Glucosidase inhibitors	53 (51.0%)	80 (44.7%)	0.31
Insulin secreting drugs	28 (26.9%)	34 (19.0%)	0.12
Dipeptidyl peptidase-4 inhibitors	11 (10.6%)	16 (8.9%)	0.65
Insulin sensitizing agents	6 (5.8%)	6 (3.4%)	0.33
Antiviral treatment, n (%)			
Arbidol	77 (74.0%)	125 (69.8%)	0.45
Lopinavir–ritonavir	25 (24.0%)	29 (16.2%)	0.11
Chloroquine/hydroxychloroquine	8 (7.7%)	11 (6.1%)	0.62
Ribavirin	12 (11.5%)	15 (8.4%)	0.38
Interferon	10 (9.6%)	14 (7.8%)	0.60
Chinese traditional medicine	79 (76.0%)	120 (67.0%)	0.11
Antibacterial treatment, n (%)	72 (69.2%)	124 (69.3%)	0.99
Anticoagulants, n (%)	26 (25.0%)	61 (34.1%)	0.11
Glucocorticoids, n (%)	40 (38.5%)	65 (36.3%)	0.72
Statins, n (%)	20 (19.2%)	35 (19.6%)	0.95

Acta Diabetologica
https://doi.org/10.1007/s00592-020-01539-z

PERSPECTIVES

Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19

Sebastiano Bruno Solerte[1] · Antonio Di Sabatino[2] · Massimo Galli[3,4] · Paolo Fiorina

Received: 9 April 2020 / Accepted: 18 April 2020

DPP4I in covid patient with/without DM may reduce virus entry/replication into airways , hamper sustained cytokine storm , inflammation

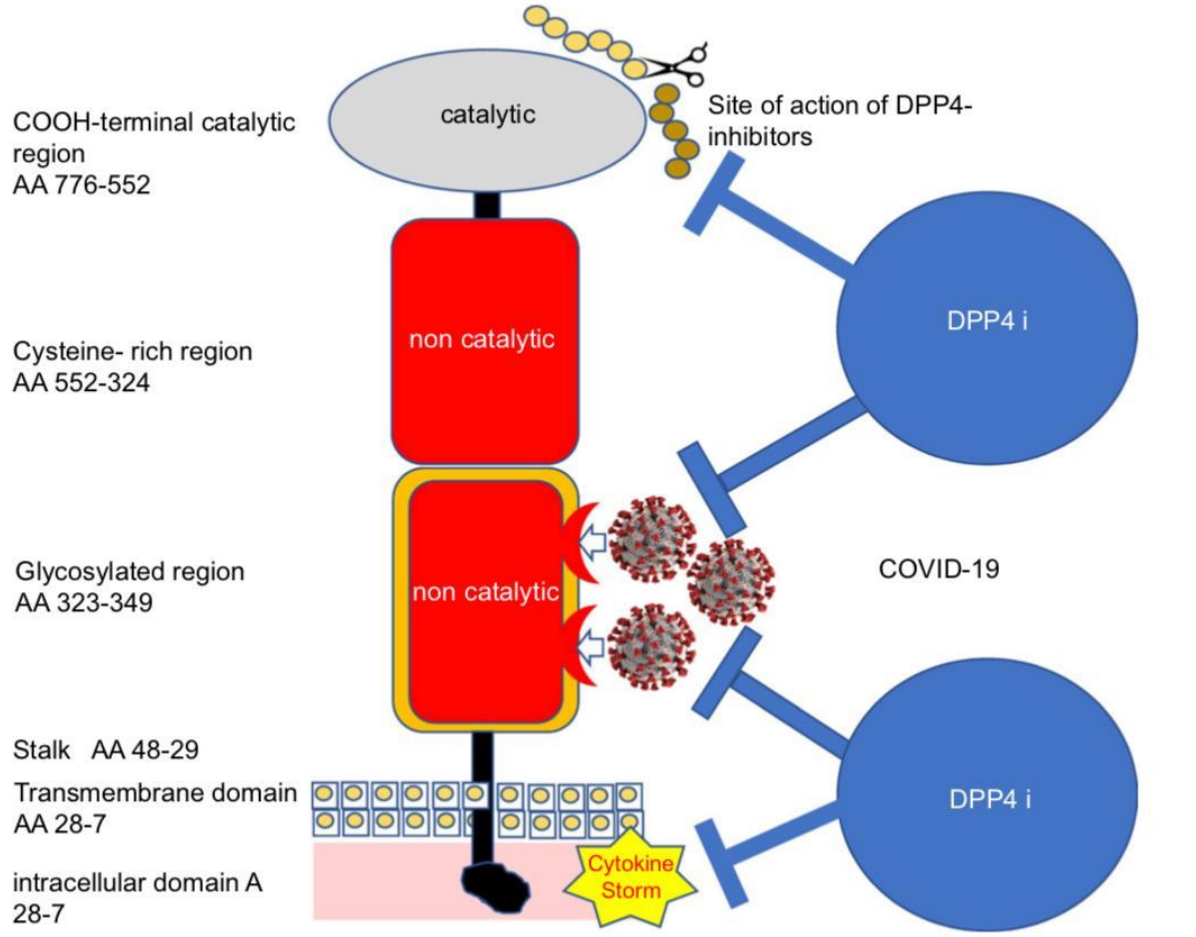

Fig. 1 Working hypothesis on the possible role of DPP4 inhibition (DPP4i) with gliptins to antagonize COVID-19 virulence and immunopathology

Journal of *Clinical Medicine*

MDPI

Review

Exploring Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors for Organ Protection in COVID-19

**Beatriz Fernandez-Fernandez [1,2], Luis D'M
Mehmet Kanbay [6], Sergio Luis-Lima [1,2], E
María José Soler [2,5] and Alberto Ortiz [1,2,*]**

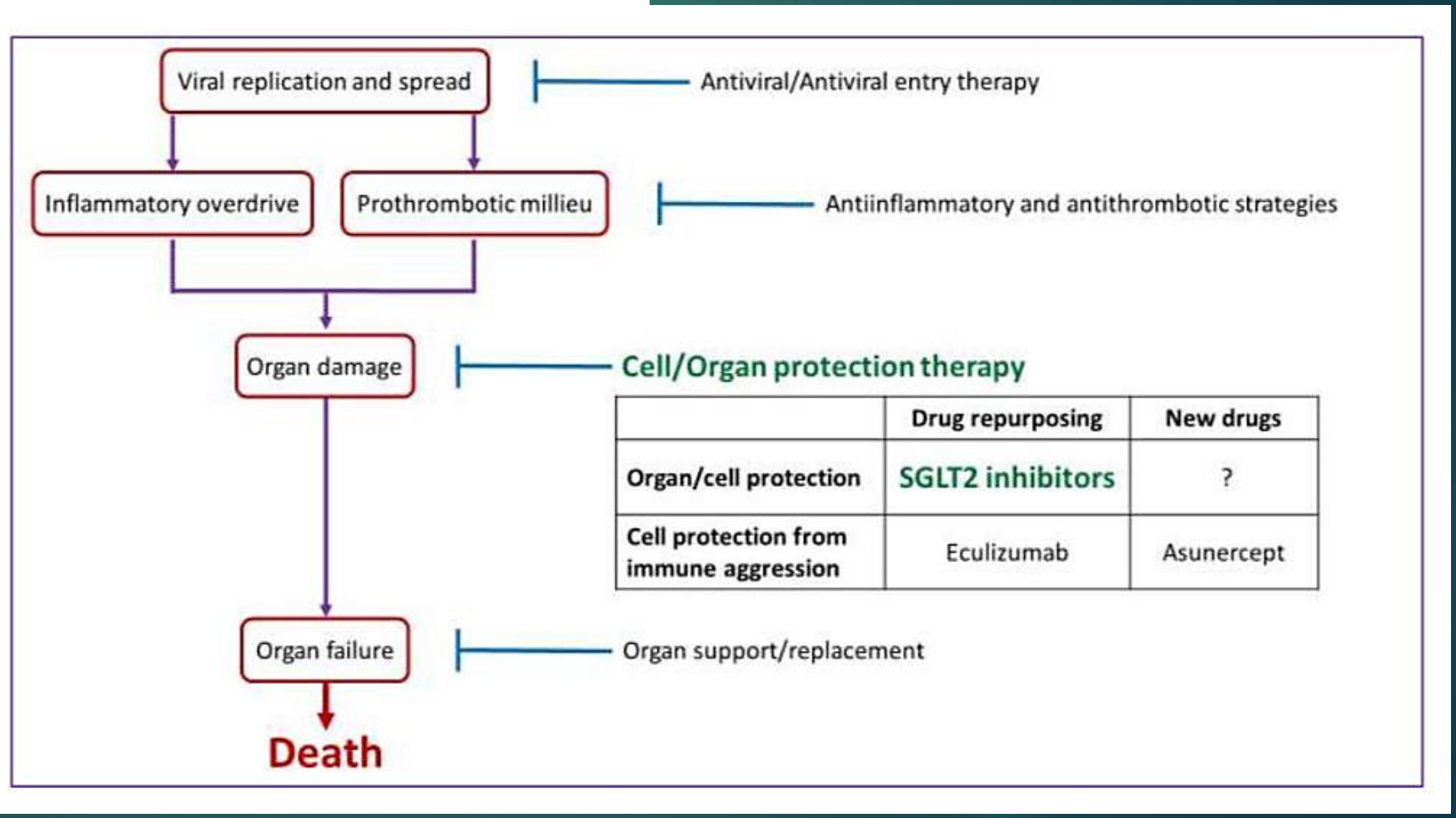

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Table 1. SGLT2 Inhibitors and COVID-19.

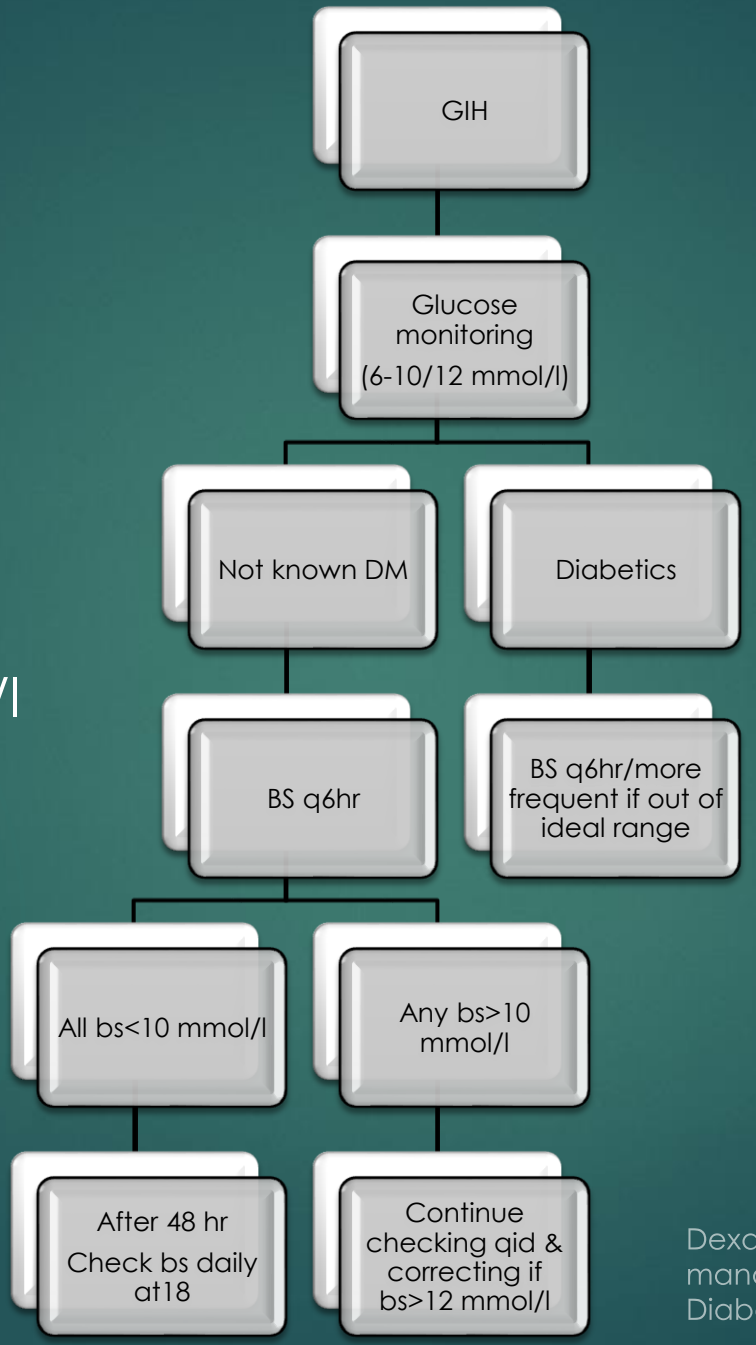
Current Status	Potential for the Future
• Health agencies recommendation to avoid SGLT2 inhibitors during COVID-19 ("sick day rules") • Risk of volume depletion • Hypotension • Ketoacidosis • Potential drug interactions (canagliflozin and lopinavir/ritonavir)	• SGLT2 inhibitors and organ protection in diabetes and outside diabetes • Clinical: heart failure, CKD • Preclinical: lung • Ongoing RCT to assess organ protection in COVID-19

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
- What are the cause of hyperglycemia in covid-19?
- How glycemic control can influence COVID mortality?
- What are the glycemic target in COVID patients?
- What are the effective treatments in out patients & hospitalized patients?
- How should GIH be managed?
- What is the prognosis of DKA in covid-19
- How should DKA be prevented/treated?

Glucocorticoid induced hyperglycemia

- Targeted glucose level:6-10/12 mmol/l



Dexamethasone therapy in COVID-19 patients and guidance for the management of blood glucose in people with and without diabetes. Diabetic Medicine(2020)

Correction dose of rapid acting insulin

Dexamethasone therapy in COVID-19 patients and guidance for the management of blood glucose in people with and without diabetes. Diabetic Medicine (2020)

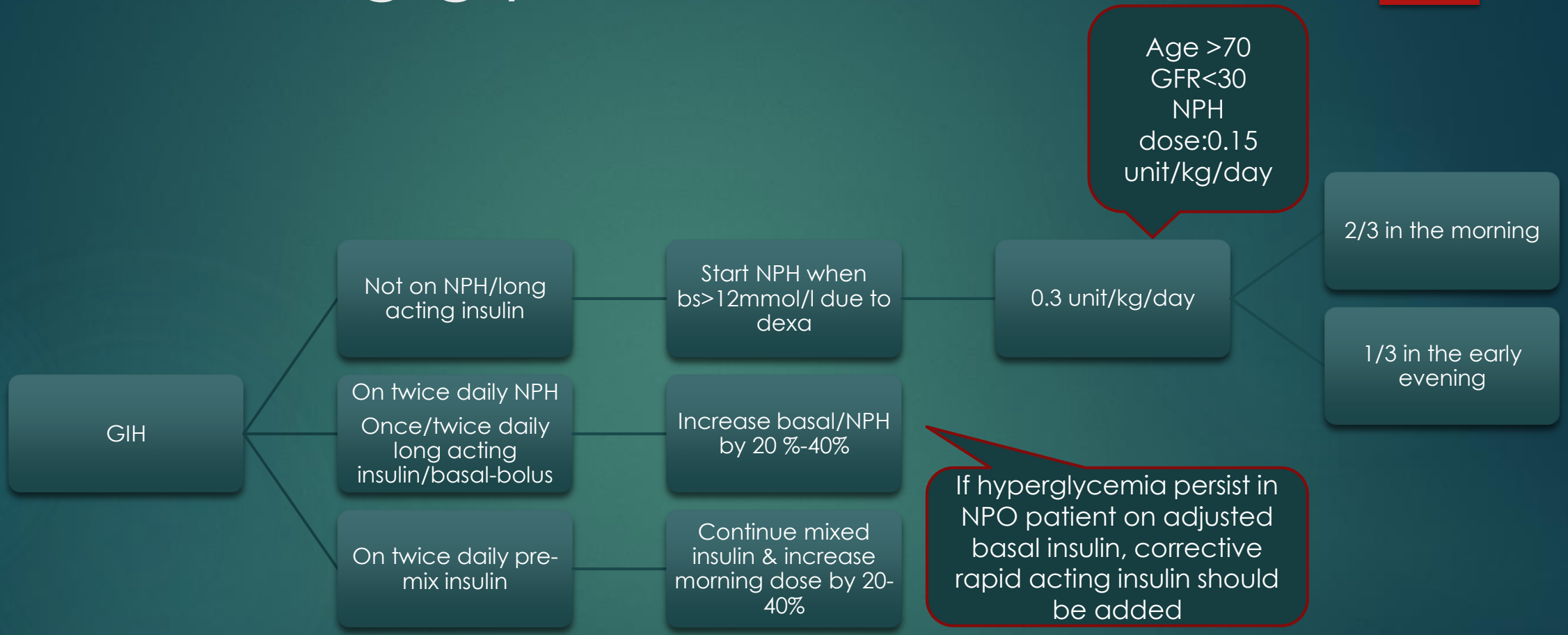
Correction dose of rapid acting insulin

CORRECTION DOSES OF RAPID ACTING INSULIN

GLUCOSE (MMOL/L)	• TDD = <50 UNITS PER DAY • OR WEIGHT < 50 KG	• TDD = 50 -100 UNITS PER DAY • OR WEIGHT 50 -100 KG	• TDD = >100 UNITS PER DAY • OR WEIGHT >100 KG	←
12.0-14.9	2 units	2 units	4 units	• Please check **KETONES** if glucose >12.0mmol/L ⚠ **If KETONE >1.5mmol/L, for doctor review** ⚠ **If KETONE >3.0mmol/L** Exclude DKA-Venous pH, bicarbonate, lab glucose, U&E. Refer to diabetes team
15.0-16.9	2 units	3 units	5 units	
17.0-18.9	3 units	4 units	5 units	
19.0-20.9	3 units	5 units	6 units	
21.0-22.9	4 units	6 units	7 units	
23.0-24.9	4 units	7 units	8 units	
25.0-27.0	5 units	8 units	9 units	
Over 27	6 units	9 units	10 units	

Dexamethasone therapy in COVID-19 patients and guidance for the management of blood glucose in people with and without diabetes. Diabetic Medicine(2020)

Maintaining glycemic control



Dexamethasone therapy in COVID-19 patients and guidance for the management of blood glucose in people with and without diabetes. Diabetic Medicine(2020)

Dose adjustment

TWICE daily NPH or long-acting insulin

GLUCOSE LEVEL	JUST BEFORE MORNING INSULIN DOSE	JUST BEFORE EVENING INSULIN DOSE
<4mmol/L	Reduce **evening** insulin by 20%	Reduce **morning** insulin by 20%
4.1-6mmol/L	Reduce **evening** insulin by 10%	Reduce **morning** insulin by 10%
6.1-12mmol/L	No change	No change
12.1-18mmol/L	Increase **evening** insulin 10%	Increase **morning** insulin by 10%
>18mmol/L	Increase **evening** insulin by 20%	Increase **morning** insulin by 20%

ONCE daily long-acting insulin

GLUCOSE LEVEL JUST BEFORE INSULIN DOSE	
<4mmol/L	Reduce insulin by 20%
4.1-6mmol/L	Reduce insulin by 10%
6.1-12mmol/L	No change
12.1-18mmol/L	Increase insulin by 10%
>18mmol/L	Increase insulin by 20%

Dexamethasone therapy in COVID-19 patients and guidance for the management of blood glucose in people with and without diabetes. Diabetic Medicine(2020)

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Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature

Rimesh Pal [a,*,1], Mainak Banerjee [b,1], Urmila Yadav [c], Sukrita Bhat

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[b] Department of Endocrinology, Institute of Post Graduate Medical Education and Research, Kolkata, 700007, Ind
[c] National Institute of Nursing Education, Post Graduate Institute of Medical Education and Research, Chandigarh
[d] Department of Hematology, Institute of Hematology and Transfusion Medicine, Medical College and Hospital, K

19 study, 110 patient
83% DKA
17% DKA,HHS(higher BS, more dehydration, higher mortality(67% vs 29%)

Table 2
Showing demographic parameters of the COVID-19 patients with DKA (and combined DKA/HHS).

Parameter	Value
Age (years) [Median (IQR)]	45.5 (36.2–57.7) [7,8,10–16,18–21,23,24,28][a]
	57.0 (48.0–64.0) [22] [b]
	59.0 (42.3–70.0) [9]
Sex (N = 102) [c]	Male (n = 64, 63%)
	Female (n = 38, 37%)
Ethnicity[d] (N = 84)	Black (n = 30, 36%) [e]
	Hispanic (n = 19, 23%)
	White (Caucasian) (n = 10, 12%)
	Asian (n = 6, 7%)
	Mixed (n = 4, 5%)
	Others (n = 8, 9%)
	Unknown (n = 7, 8%)
Type of diabetes [f] (N = 97)	Pre-existing T1DM (n = 12, 12%)
	Pre-existing T2DM (n = 74, 77%)
	Newly diagnosed (n = 10, 10%)
	Gestational DM (n = 1, 1%)
Use of SGLT2 inhibitors [g]	7
BMI (kg/m^2) [Median (IQR)]	26.6 (23.7–32.3) [7,11–13,16,28] [h]
	24.7 (21.3–28.5) [22] [b]
	27.1 (23.2–33.0) [9]

Table 3
Showing biochemical parameters at presentation in COVID-19 patients with DKA (and combined DKA/HHS).

Biochemical parameter at presentation	Value[a]
Blood glucose (mg/dl)	568.5 (385.5–889.7) [7,8,10–16,18–21,23,24,28] [b]
	486.0 (396.0–558.0) [22] [g]
	506.5 (252.0–1485.0) [9]
HbA_{1c} (%)	11.7 (9.5–13.2) [10–13,16,19,23,24,28] [c]
	12.4 (10.7–14.2) [22] [g]
pH	7.17 (6.99–7.24) [7,8,10–16,18,21,23,24,28] [d]
	7.20 (6.90–7.30) [22] [g]
Bicarbonate (mmol/l)	8.0 (6.0–12.5) [7,8,10–14,16,23,24,28] [e]
	11.8 (7.8–15.4) [22] [g]
Anion gap (mEq/l)	29.0 (18.0–32.0) [7,8,12,13,15,20,24,28] [f]
	14.8 (10.4–20.5) [22] [g]
	28.1 (14.3–41.2) [9]

Table 4
Showing comparison of clinical outcomes of COVID-19 patients with DKA (and combined DKA/HHS) in whom individual patient data were available (N = 27).

Parameter	Discharged (n = 17)	Deceased (n = 10)	*p* value
Age (years)	46.0 (33.5–54.0)	42.5 (34.2–59.7)	1.000
Sex	Male = 11 Female = 6	Male = 10 Female = 0	–
DKA vs. Combined DKA/HHS	DKA = 15 (71%) DKA/HHS = 2 (33%)	DKA = 6 (29%) DKA/HHS = 4 (67%)	–
Blood glucose (mg/dl)	463.0 (347.0–641.0)	801.5 (376.5–1080.5)	0.120
pH	7.23 (7.09–7.26)	7.00 (6.91–7.11)	**0.017**
Bicarbonate (mmol/l)	10.4 (6.0–15.0)	7.0 (5.7–8.0)	0.098
Anion gap (mEq/l)	25.5 (16.8–34.0)	29.0 (28.0–30.5)	0.806

COVID-19: Novel coronavirus disease; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome.

questions

- Who are high risk patient for corona viruses?
- Are all diabetics are similar in facing COVID 19?
- How hyperglycemia affect immune system?
- What are the cause of hyperglycemia in covid-19?
- How glycemic control can influence COVID mortality?
- What are the glycemic target in COVID patients?
- What are the effective treatments in out patients & hospitalized patients?
- How should GIH be managed?
- What is the prognosis of DKA in covid-19
- How should DKA be prevented/treated?

DKA prevention in COVID

B. INSULIN REDUCTION NORMOGLYCEMIA/HYPOGLYCEMIA			
KETONES (starvation)		BLOOD GLUCOSE	
BLOOD	URINE	< 5,0 mmol/L < 90 mg/dL	5,0 - 10 mmol/L 90 - 180 mg/dL
< 0,6 mmol/L	Negative/trace	• No extra insulin • Reduce TDD insulin 20% • Oral sugar fluids and extra CHO (*) • If BG < 70mg/dl → Hypo correction (consider mini-dose of glucagon)	• No extra insulin
0,6 – 0,9 mmol/L	Trace/small	• Reduce TDD insulin 15% • Give ordinary bolus • Oral sugar fluids • Extra CHO (*)	• Oral sugar fluids • Extra CHO (*)
1 – 1,4 mmol/L	small/moderate	• Reduce TDD insulin 10% • Give ordinary bolus • Oral sugar fluids • Extra CHO (*)	• Give ordinary bolus • Oral sugar fluids • Extra CHO (*)
1,5 – 2,9 mmol/L	Moderate/large	• Do not reduce TDD insulin • Give ordinary bolus • Oral sugar fluids • Extra CHO (*) • If vomiting, cannot eat or drink, consider IV Saline +5% glucose solution	• Add +5% TDD or 0,05 U/Kg to ordinary bolus • Oral sugar fluids • Extra CHO (*)
≥ 3 mmol/L	large		• Add +5% TDD or 0,05 U/Kg to ordinary bolus
		Risk of Ketoacidosis	
CHECK FOR BG AND KETONES EVERY 2 HOURS			

Sick day Management in Children and Adolescents with Diabetes . ISPAD Clinical Practice Consensus Guidelines 2018

DKA treatment in COVID

Table 1. Classification of hyperglycemic crisis severity (10) and insulin treatment options

	Mild DKA	Moderate DKA	Severe DKA	HHS	HK
Blood glucose mg/dL (mmol/L)	> 250 (>13.8)	>250 (>13.8)	>250 (>13.8)	>600 (>33.3)	>600 (>33.3)
pH	7.25-7.30	7.00-7.24	<7.00	>7.30	
HCO_2 (mmol/L)	15-18	10-14	<10	>18	
Urine/serum ketones	+	+	±	±	+
Serum osmolality[a] (Osm_{eff})				320	320
Anion gap	Elevated	Elevated	Elevated	Elevated	Elevated
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma	Stupor/coma
Insulin therapy	SC/IV	SC/IV	IV	IV	IV
Frequency of glucose monitoring	every 1-2 hours	every 1-2 hours	every 1 hour	every 1 hour	every 1 hour
Location of care	Intermediate care unit	Intermediate care unit/ICU	ICU	ICU	ICU

Diabetic Ketoacidosis in COVID-19:Uniqe Concerns and Considerations .J Clin Endocrinol Metab(2020)


THANK
YOU

Table 2

DETAILED TREATMENT GUIDANCE BG 200–250 mg/dL		
1.	**NO PRIOR KNOWN DIABETES or KNOWN DIABETES ON <2 ORAL AGENTS**	**MONITORING**
	• Check HbA_{1c} if none available in last 3 months	Check BG every 6 h
a	**Start sliding scale** regular insulin: moderate to high dose and escalate scale if BG >250 mg/dL	
b	**Add scheduled regular insulin every 6 h** if TF initiated (see above for regular insulin dosing based on eGFR and hourly TF rate) + scale	
c	**Add scheduled regular insulin if BG remains>250 mg/dL +** scale even if no TF initiated	
2.	**KNOWN DIABETES PRIOR TO ADMISSION**	Check BG every 6 h
	• Check HbA_{1c} if none available in last 3 months	
a	**T1DM** NPO: **add basal insulin glargine** ASAP (to **avoid DKA**): use 70% of home dose if eGFR >50 and 50% if eGFR <50 **+ scale**	
b	**T1DM on insulin pump and has supplies:** if feasible, continue basal insulin via pump (use increased temporary basal rate if needed); **rare use in ICU so calculate total basal as in a**	
c	**T1DM + TF:** continue basal insulin (to prevent DKA) and add **scheduled regular insulin for TF every 6 h** (guidance above based on eGFR and TF rate) + scale	
d	**T2DM NPO:** on regimen that included insulin prior to admission: start 25–50% basal dose + scale	
e	**T2DM on insulin PTA + TF:** start 25–50% basal dose and regular insulin for TF coverage every 6 h; see above for dose calculations + scale	

BG, blood glucose; DKA, diabetes ketoacidosis; eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); HbA_{1c}, hemoglobin A_{1c}; NPO, nothing by mouth; PTA, prior to admission; T1DM, patients with type 1 diabetes; T2DM, patients with type 2 diabetes; TF, tube feeding.

Table 1—Initial subcutaneous insulin dosing guideline for critically ill COVID-19 patients admitted with high glucose

BG 200–250 mg/dL*: see details of treatment and titration in Table 2				
a	**START SLIDING SCALE REGULAR** insulin: moderate to high dose scale			**MONITORING**
b	**ADD SCHEDULED REGULAR INSULIN** every 6 h if uncontrolled with scale or if tube feeds started			BG check every 6 h
c	**ADD BASAL INSULIN GLARGINE for patients with the following:**			
	• T1DM (70% of home dose for eGFR >50 and 50% for eGFR <50 to avoid DKA)			
	• T2DM on home insulin (25–50% basal dose) or >2 drugs			
	• Uncontrolled glucose on regular insulin alone: use 0.1–0.3 units/kg daily (below)			
	• NPH may be appropriate basal for patients on steroids			
BG 250–350 mg/dL: START SCHEDULED SUBCUTANEOUS INSULIN				
		HIGH SENSITIVITY No known diabetes, known DM with renal failure (eGFR<30), insulin naive, mild disease*	**MODERATE SENSITIVITY Known DM, renal failure (eGFR 30–50), intermediate disease course****	**LOW SENSITIVITY Known DM, renal function (eGFR >50), steroids, severe disease*****
Type of insulin		**Insulin dose (units/kg)**		
BASAL#	**Glargine daily: noon or 6 P.M.**	0.1 units/kg/day	0.15–0.2 units/kg/day	0.3 units/kg/day
BOLUS	**Scheduled regular insulin every 6 h**	**Approximate start doses (units/kg every 6 h); use clinical judgement**		
	No tube feeds	0.1	0.15	0.2
	Low rate tube feeds (≤25 cc/h)	0.1–0.125	0.1–0.15	0.2–0.25
	High rate tube feeds (≥25 cc/h)	0.15	0.2	0.3
SCALE	**Regular insulin every 6 h**	Moderate	Moderate	High
FOLLOW TRENDS IN INFLAMMATORY MARKERS: PROCALCITONIN, D-DIMER, hsCRP, AND TRIGLYCERIDES TO GUIDE IN UPWARD or DOWNWARD TITRATION OF INSULIN DOSE				
BG >350 mg/dL: INSULIN INFUSION NOT INITIATED or VARIABLE INFUSION RATES HARD TO TRANSITION				
Regular insulin	**BG (mg/dL)**	**Give subcutaneous regular insulin dosed as below:**		**MONITORING**
1st dose	350–450	0.2 units/kg		After 2 h
	>450	0.3 units/kg		
2nd dose	250–350	None		After 4 h
	350–450	Give 50% original dose		
	>450	Redose original dose calculated in 1		
3rd dose	<250	Maintain current dose + add low dose sliding scale		After 6 h
	250–350	Increase current dose 10% + add moderate dose sliding scale		
	350–450	Increase current dose 20% + add moderate dose sliding scale		
	>450	Increase current dose 30% + add moderate dose sliding scale		
≥4 doses	Titrate dose in 3 as per BG and order as scheduled regular			Every 6 h
BASAL INSULIN: #as above				
BG >350 mg/dL: TRANSITIONING FROM INSULIN INFUSION WITHIN A FEW HOURS VERY QUICKLY WITH SUBCUTANEOUS REGULAR INSULIN				
REGULAR insulin	**BG (mg/dL)**			**MONITORING**
1st dose	Calculate average hourly drip rate for 2 h			After 2 h
	Multiply average hourly drip rate × 3			
	Give that dose as subcutaneous regular insulin stat; **stop insulin drip**			
2nd dose	<70: hypoglycemia protocol			After 4 h
	70–150: reduce dose by 50%			
	150–350: no intervention			
	>350: repeat original dose of regular insulin			
3rd dose	<70: hypoglycemia protocol			After 6 h
	70–150: reduce dose by 50% + add moderate dose sliding scale			
	150–350: continue original dose + add moderate dose sliding scale			
	>350: increase original dose by 50% + add high dose sliding scale			
≥4 doses	Titrate dose in 3 as per BG and order as scheduled regular			Every 6 h
BASAL INSULIN: #as above				
BG >450 mg/dL: SHORT DURATION OF INSULIN INFUSION TILL DRIP RATE STABILIZES				

Table 1—Initial subcutaneous insulin dosing guideline for critically ill COVID-19 patients admitted with high glucose

BG 200–250 mg/dL*: see details of treatment and titration in Table 2				
a	**START SLIDING SCALE REGULAR** insulin: moderate to high dose scale			**MONITORING**
b	**ADD SCHEDULED REGULAR INSULIN** every 6 h if uncontrolled with scale or if tube feeds started			BG check every 6 h
c	**ADD BASAL INSULIN GLARGINE for patients with the following:**			
	• T1DM (70% of home dose for eGFR >50 and 50% for eGFR <50 to avoid DKA)			
	• T2DM on home insulin (25–50% basal dose) or >2 drugs			
	• Uncontrolled glucose on regular insulin alone: use 0.1–0.3 units/kg daily (below)			
	• NPH may be appropriate basal for patients on steroids			
BG 250–350 mg/dL: START SCHEDULED SUBCUTANEOUS INSULIN				
		HIGH SENSITIVITY **No known diabetes, known DM with** renal failure (eGFR<30), insulin naive, mild disease*	**MODERATE SENSITIVITY** **Known DM,** renal failure (eGFR 30–50), intermediate disease course**	**LOW SENSITIVITY** **Known DM,** renal function (eGFR >50), steroids, severe disease***

Type of insulin		Insulin dose (units/kg)		
BASAL#	**Glargine daily: noon or 6 P.M.**	0.1 units/kg/day	0.15–0.2 units/kg/day	0.3 units/kg/day
BOLUS	**Scheduled regular insulin every 6 h**	**Approximate start doses (units/kg every 6 h); use clinical judgement**		
	No tube feeds	0.1	0.15	0.2
	Low rate tube feeds (≤25 cc/h)	0.1–0.125	0.1–0.15	0.2–0.25
	High rate tube feeds (≥25 cc/h)	0.15	0.2	0.3
SCALE	**Regular insulin every 6 h**	Moderate	Moderate	High
FOLLOW TRENDS IN INFLAMMATORY MARKERS: PROCALCITONIN, D-DIMER, hsCRP, AND TRIGLYCERIDES TO GUIDE IN UPWARD or DOWNWARD TITRATION OF INSULIN DOSE				

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Regular insulin	**BG (mg/dL)**	**Give subcutaneous regular insulin dosed as below:**	**MONITORING**
1st dose	350–450	0.2 units/kg	After 2 h
	>450	0.3 units/kg	
2nd dose	250–350	None	After 4 h
	350–450	Give 50% original dose	
	>450	Redose original dose calculated in 1	
3rd dose	<250	Maintain current dose + add low dose sliding scale	After 6 h
	250–350	Increase current dose 10% + add moderate dose sliding scale	
	350–450	Increase current dose 20% + add moderate dose sliding scale	
	>450	Increase current dose 30% + add moderate dose sliding scale	
≥4 doses	Titrate dose in 3 as per BG and order as scheduled regular		Every 6 h

BASAL INSULIN: #as above		
BG >350 mg/dL: TRANSITIONING FROM INSULIN INFUSION WITHIN A FEW HOURS VERY QUICKLY WITH SUBCUTANEOUS REGULAR INSULIN		
REGULAR insulin	**BG (mg/dL)**	**MONITORING**
1st dose	Calculate average hourly drip rate for 2 h	After 2 h
	Multiply average hourly drip rate × 3	
	Give that dose as subcutaneous regular insulin stat; **stop insulin drip**	
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	150–350: no intervention	
	>350: repeat original dose of regular insulin	
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