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COVID-19

Update

September 23

Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study

- **Methods**
 - A real-time search to the electronic medical records of more than 49 million non-identified patients from 37 health care organizations in the US
 - Identified patients with COVID-19 were then stratified into 2 groups
 - Liver Disease (LD) defined as a diagnosis of chronic liver disease or cirrhosis
 - No liver disease (NLD)
- **Outcomes**
 - Mortality, hospitalization, and laboratory findings in the time window up to 30 days from the diagnosis of COVID-19

Table 1. Outcomes and Baseline Characteristics Among Patients With COVID-19 Stratified Into Those With Preexisting Liver Disease and Without Liver Disease

	Before propensity matching			After propensity matching		
	COVID-19 with liver disease (n = 250)	COVID-19 without liver disease (n = 2530)	RR, RD, or P value	COVID-19 with liver disease (n = 250)	COVID-19 without liver disease (n = 250)	RR, RD, or P value
Outcomes						
Mortality, %, (n/total)	12.0 (30/250)	4.3 (110/2530)	RR: 2.8 (1.9, 4.0) RD: 7.7% (3.5%, 11.75%) P < .001	12.0 (30/250)	4.0 (10/250)	RR: 3.0 (1.5, 6.0) RD: 8.0% (3.3%, 12.7%) P = .001
Hospitalization rate	52.0 (130/250)	30.0 (760/2530)	RR: 1.7 (1.2, 2.0) RD: 22.0% (15.5%, 28.4%) P < .001	48.0 (120/250)	36.0 (90/250)	RR: 1.3 (1.1, 1.6) RD: 12.0% (3.4%, 20.6%) P = .006
Characteristics						
Age, y, mean ± SD	55.2 ± 14.6	51.6 ± 17.8	<.01	55.4 ± 14.4	56.7 ± 15.3	.36
Female, n (%)	140 (56)	1570 (62)	.06	140 (56)	140 (56)	1.00
Race: white, n (%)	130 (52)	1220 (48.2)	.25	130 (52)	130 (52)	1.00
Nicotine dependence, n (%)	60 (24)	190 (7.5)	<.01	50 (20)	50 (20)	1.00
Body mass index >30.0 to 30.9 kg/m ² , n (%)	60 (24)	310 (12.5)	<.01	50 (20)	50 (20)	1.00
Race: black or African American, n (%)	100 (40)	1000 (39.5)	.88	100 (40)	110 (44)	.36
Hypertension, n (%)	170 (68)	1020 (40.3)	<.01	170 (68)	170 (68)	1.00
Diabetes mellitus, n (%)	120 (48)	520 (14.8)	<.01	110 (44)	110 (44)	1.00
Chronic lower respiratory diseases, n (%)	100 (40)	280 (11.0)	<.01	100 (40)	70 (28)	.01
Chronic kidney disease, n (%)	80 (32)	305 (7.2)	<.01	80 (32)	50 (20)	.01
Heart failure, n (%)	60 (24)	220 (8.7)	<.01	60 (24)	50 (20)	.28

NOTE. Outcomes and baseline characteristics are compared before and after propensity score matching of groups.

Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study

- **A total of 2780 patients with COVID-19 were identified**
 - **LD:** 250 (9%) patients, **NLD:** 2530 (89%)
- ALT and AST were elevated after COVID-19 in both groups
- **Patients in the LD group had:**
 - Significantly higher risk of mortality
 - **RR, 2.8;** (95% CI,1.9–4.0; P < .001)
 - Higher risk of hospitalization
 - **RR, 1.7** (95% CI,1.2–2.0; P < .001)
 - Patients with cirrhosis had an even higher mortality
 - **RR, 4.6;** (95% CI, 2.6–8.3; P < .001).

Conclusions

- Liver injury can be seen in most patients with COVID-19
- Patients with preexisting liver disease, notably cirrhosis, are at higher risk for hospitalizations and mortality
- Early isolation, intensive surveillance, and timely diagnosis are essential in these patients
- Further research identifying interventions to reduce poor outcomes in high-risk patients with COVID-19 is needed

Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women

METHODS

- Women in the US having a confirmed SARS-CoV-2 infection and concurrently breastfeeding were invited to participate in the study
- Breast milk samples were self-collected and mailed to the study center
- A SARS-CoV-2 RT-PCR in breast milk as well as tissue culture was validated
- Conditions of pasteurization commonly used in human milk banks were mimicked

Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women:

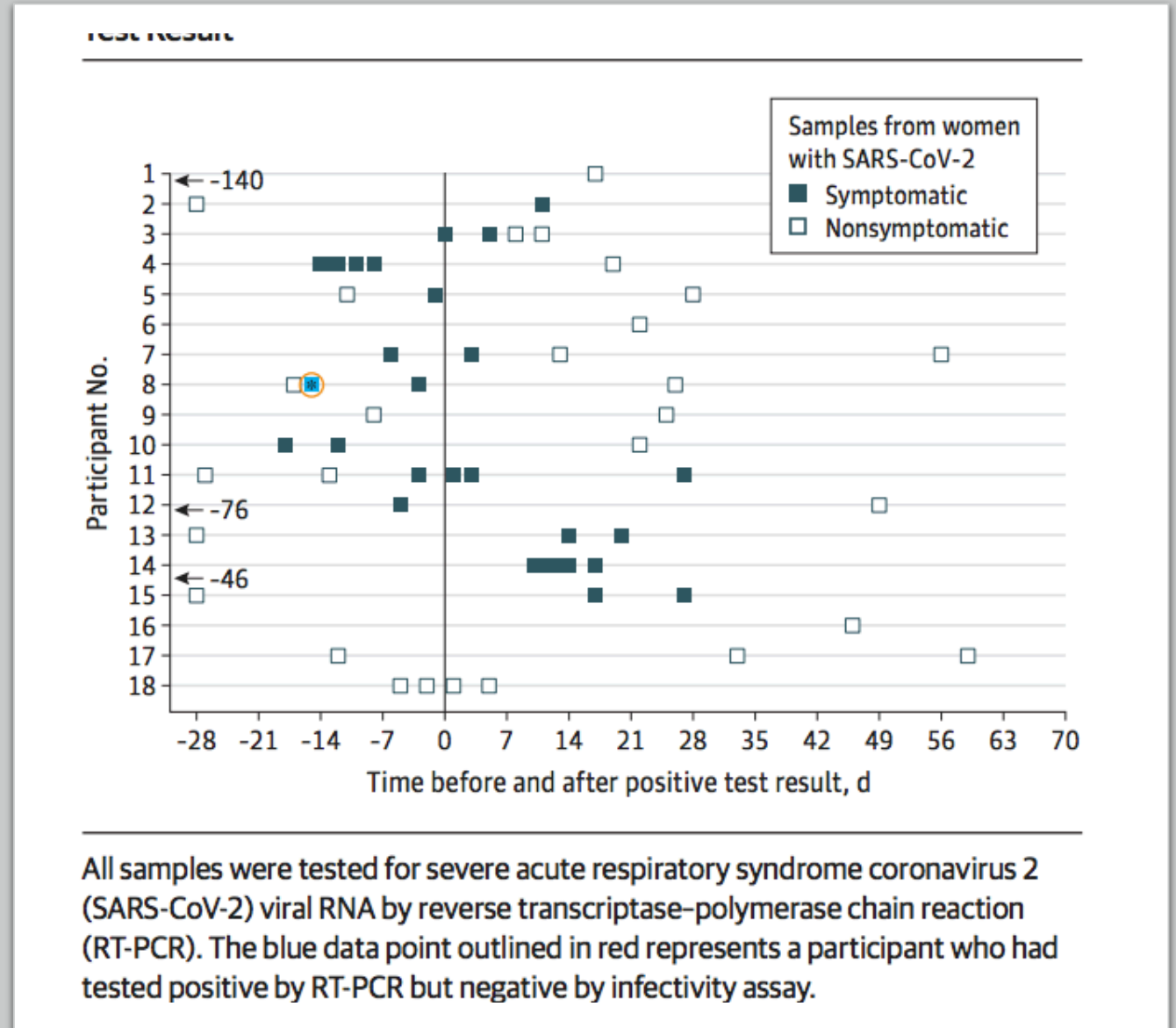
RESULTS

- **Eighteen women with confirmed SARS-CoV-2 infection enrolled**
 - 77.7% White non-Hispanic, mean age 34.4 years [SD, 5.2 years]
 - Their offspring ranged in age from newborn to 19 months
 - A total of 64 samples collected before and after the positive SARS-CoV-2 RT-PCR test.

Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women

RESULTS

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Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women:

RESULTS

- **One breast milk sample had detectable SARS-CoV-2 RNA**
 - Positive sample collected on the day of symptom onset;
 - 1 sample taken 2 days prior to symptom onset and 2 samples collected 12 and 41 days later tested negative
- **No replication-competent virus** was detectable in any sample
- **Pasteurized aliquots**
 - Viral RNA not detected in the spiked milk samples
 - No culturable virus detected in the spiked milk samples
- **Non pasteurized aliquots**
 - Virus was detected by culture in one of the same 2 milk-virus mixtures.

Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women

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- SARS-CoV-2 RNA was detected in 1 sample, but the culture was negative
- Breast milk may not be a source of infection for the infant
- When control samples spiked with RCV were pasteurized, no RCV or viral RNA was found
- Limitations
 - Small sample size
 - Nonrandom sample
 - Self-report of RT-PCR positivity
 - Self-collection of milk samples

RCV: replication competent virus

Probative Value of the d-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome

METHODS

- Only patients with confirmed SARS-CoV-2 infection by RT PCR included
- Serial d-dimer, troponin-I, LDH, C-reactive protein (CRP), interleukin (IL)-6, and fibrinogen
- Assessment for LeDVT with two clinical prediction tools used (Wells score and the Dutch Primary Care Rule)
- LeDVT US done in those patients with a positive screening prediction tool

LeDVT: Lower extremity Deep Vein Thrombosis

Probative Value of the d-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome

RESULTS

- Seventy-two patients with severe COVID-19 had 102 Lower extremity US performed
- Twelve patients (17%) developed LeDVT.
- Screening tools were not useful
- Except for d-dimer, not other marker discriminated between patients with and without a LeDVT
- Using a d-dimer cutoff value of 3,000 ng/mL
 - Sensitivity was 100%, specificity was 51.1%
 - PPV was 21.8%, NPV was 100%

TABLE 1. Demographics, Inflammatory Biomarkers, and Renal Function Variables

Variable (Normal Reference)	Overall	Lower Extremity Deep Venous Thrombosis (n = 12)	No Evidence of Deep Venous Thrombosis (n = 60)
Age	64	66.2	63.7
% Male	79	75	80
% Mortality	24	8	27
C-reactive protein (≤ 0.9 mg/dL)			
Median	173	21.8	14.1
IQR	7.9–26.7	15–32.2	6.5–24.8
% Positive		100	96
D-dimer (0–229ng/mL) ^a			
Median	2,512	12,858	2,087
IQR	727–4,491	3,176–30,770	638–3,735
% Positive		100	99
Fibrinogen (180–400mg/dL)			
Median	578	570	585
IQR	483–793	503–813	460–761
% Positive		91	85
Interleukin-6 (≤ 5 pg/mL)			
Median	275	20	36.5
IQR	15–1175	13.8–49.3	15–121.8
% Positive		100	91
Creatinine (0.64–1.27 mg/dL)			
Median	1.04	1.37	1.04
IQR	0.69–1.92	0.61–1.88	0.71–1.97
% Positive		50	57
Glomerular filtration rate (≥ 60 mL/min)			
Median	64	60	64
IQR	34–101	32–113	34–100
% Positive		50	52

% Positive = proportion of tested patients with values exceeding the upper limit of the reference range, IQR = interquartile range.

^a $p < 0.0001$ by Mann-Whitney *U* test.

Median values are shown for laboratory data. Values other than D-dimer showed no statistical significance.

Conclusions

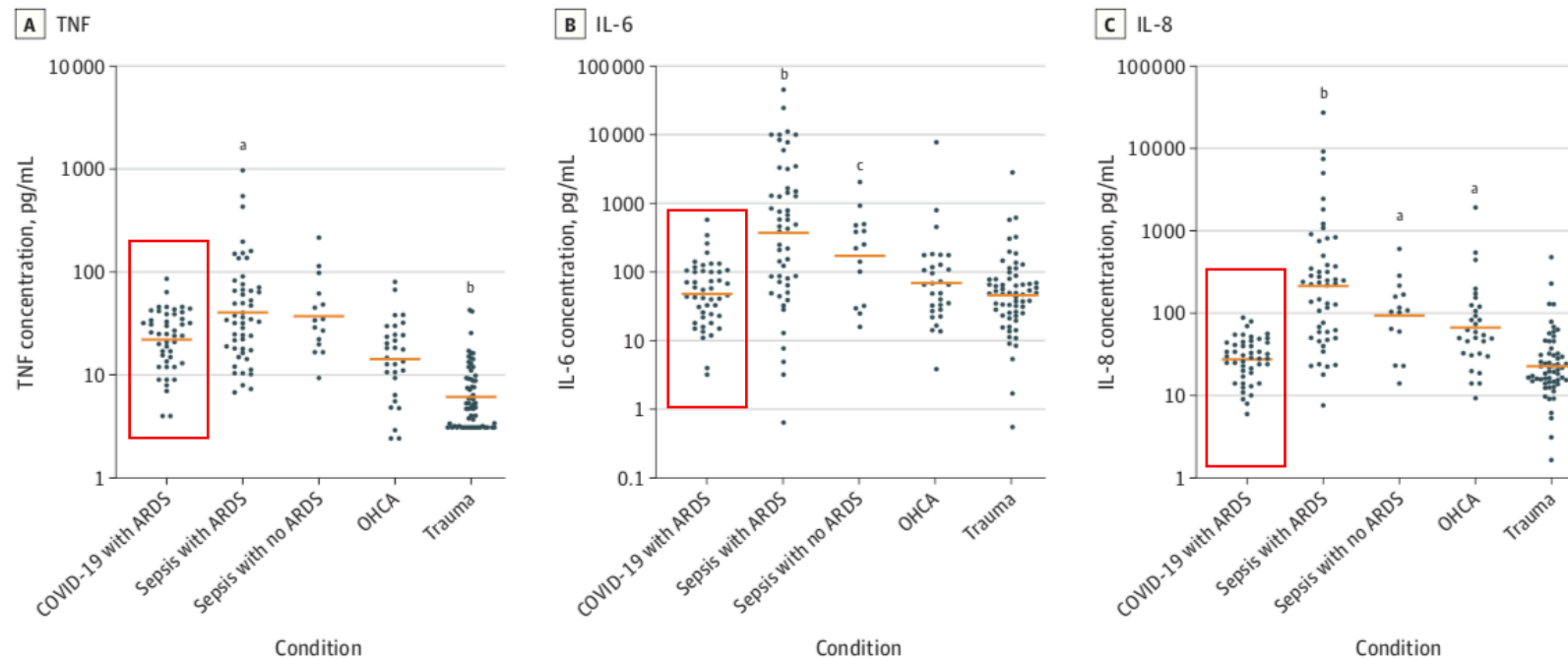
- Patients with severe COVID-19 are at increased risk for VTE
- D-dimer concentration less than 3,000ng/mL is sensitive to preclude further investigation for LeDVT
- Considering the high risk for VTE posed by COVID-19, we recommend aggressive anticoagulation in severe cases.

VTE: Venous Thromboembolism

Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions

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Figure. Cytokine Levels in Critically Ill Patients With Coronavirus Disease 2019 (COVID-19) and Other Conditions



Plasma concentrations of tumor necrosis factor (TNF) (A), IL-6 (B), and IL-8 (C) in patients with COVID-19 and acute respiratory distress syndrome (ARDS) (n = 46), septic shock with ARDS (n = 51), septic shock without ARDS (n = 15), out-of-hospital cardiac arrest (OHCA; n = 30), and multiple traumas (n = 62). Data are presented as scatter plots with red horizontal bars indicating the geometric mean levels.








^a $P < .01$ vs COVID-19 with ARDS.

^b $P < .001$ vs COVID-19 with ARDS.

^c $P < .05$ vs COVID-19 with ARDS.

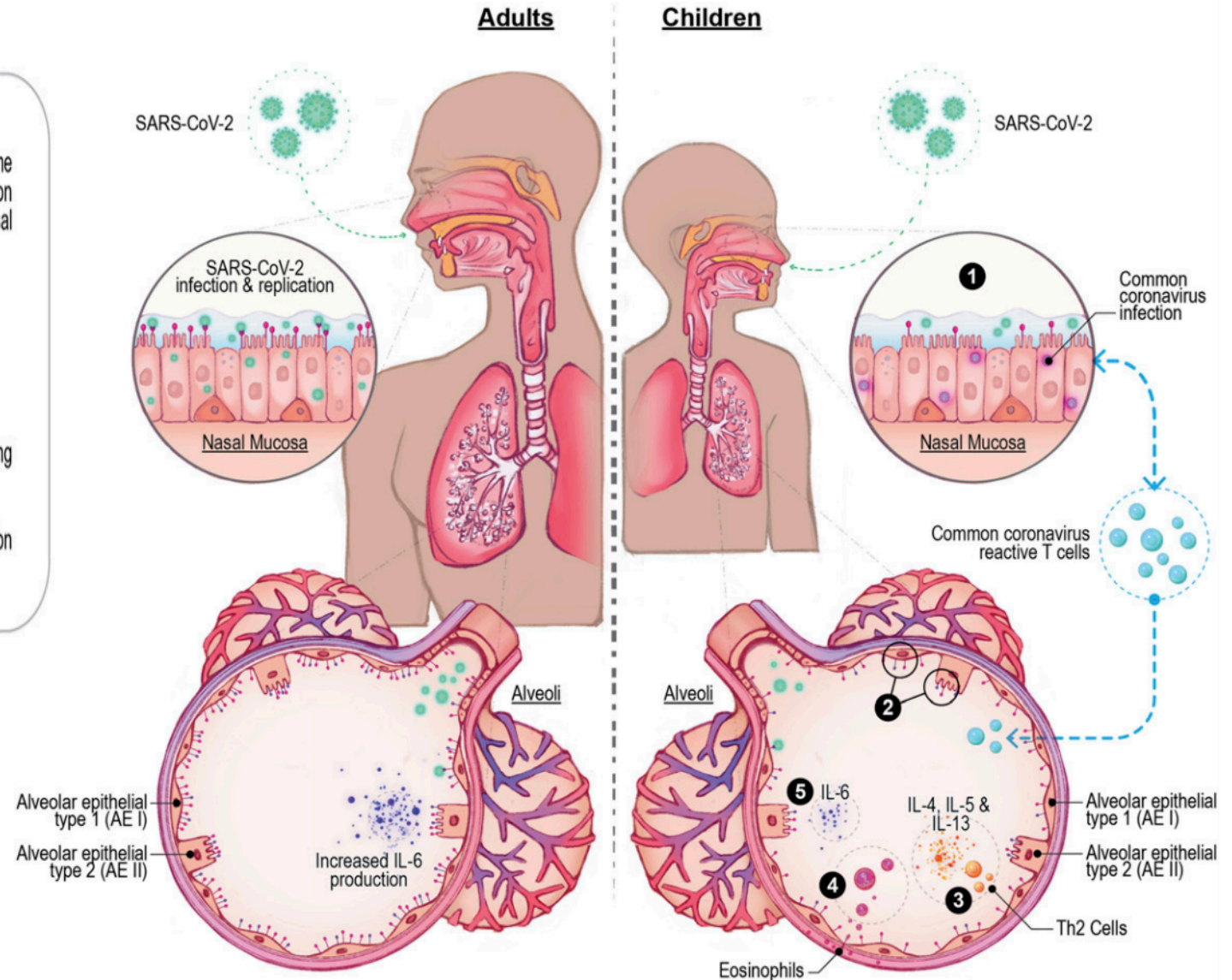
Five Clues Why Children Have Reduced Susceptibility to COVID-19

Legend

-  SARS-CoV-2 Virus
-  Common Coronavirus
-  ACE2
-  TMPRSS2
-  T helper cells (Th2)
-  Common coronavirus reactive T cells
-  Eosinophil

- 1** Coronavirus associated with common colds in children may offer some protection, due to cross-reactive T cell immunity between common coronaviruses and SARS-CoV-2, and due to reduced ACE2 in nasal mucosa of children.
- 2** Reduced TMPRSS2 in children in type I alveolar epithelial cells (AEI). Reduced ACE2 in children in type II alveolar epithelial cells (AEII).
- 3** Protective Th2 immunity in children.
- 4** Surprising protection from eosinophilia driven by Th2 cytokines including IL-4, IL-5, and IL-13 (for example childhood asthma).
- 5** Children produce lower levels of inflammatory cytokines, IL-6 production increases with age.

- Viral interference
- Immunological interference



Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics

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