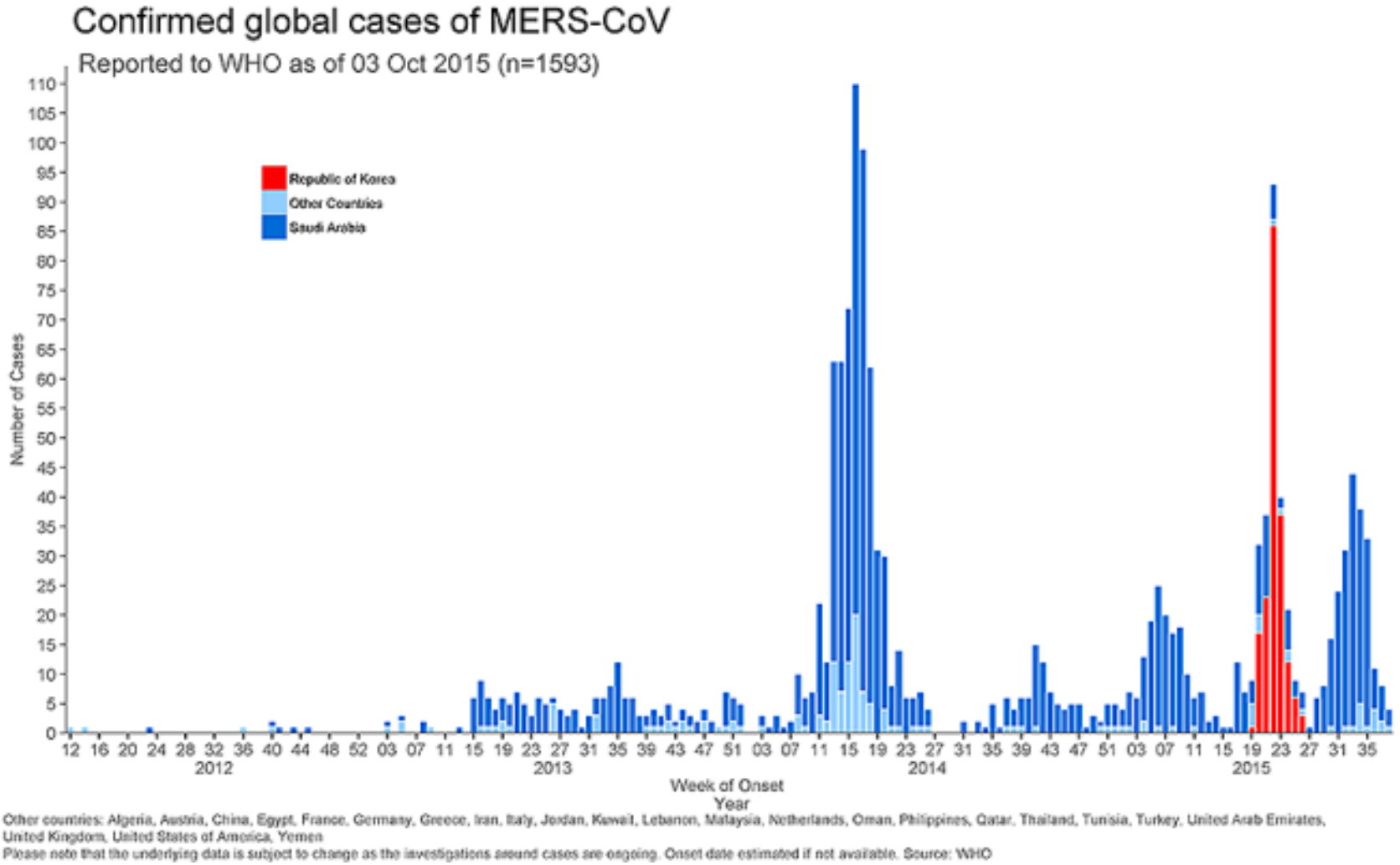
2015 MERS in KOREA

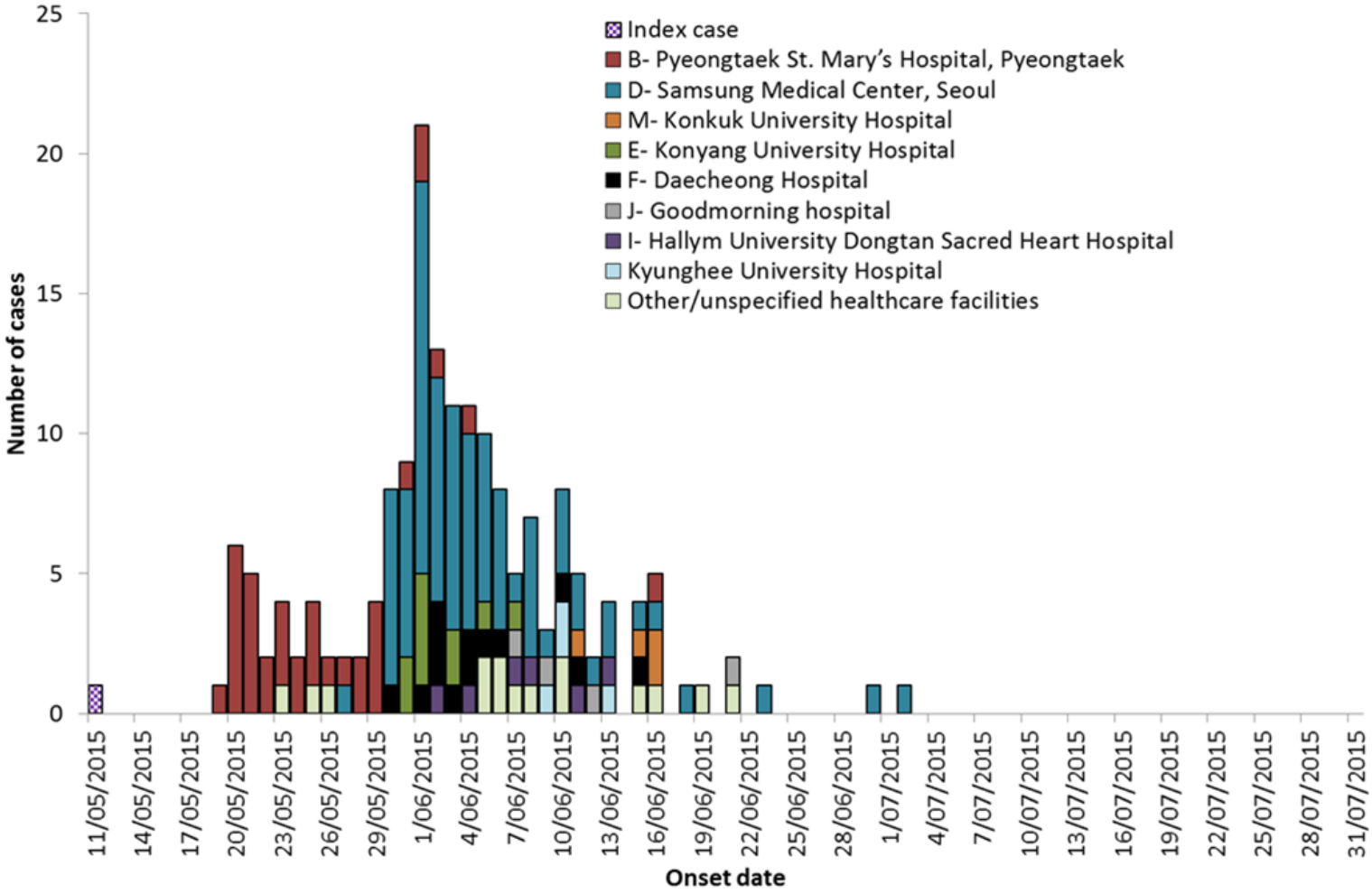
National Medical Center
Joh, Joonsung

2015 MERS in Korea



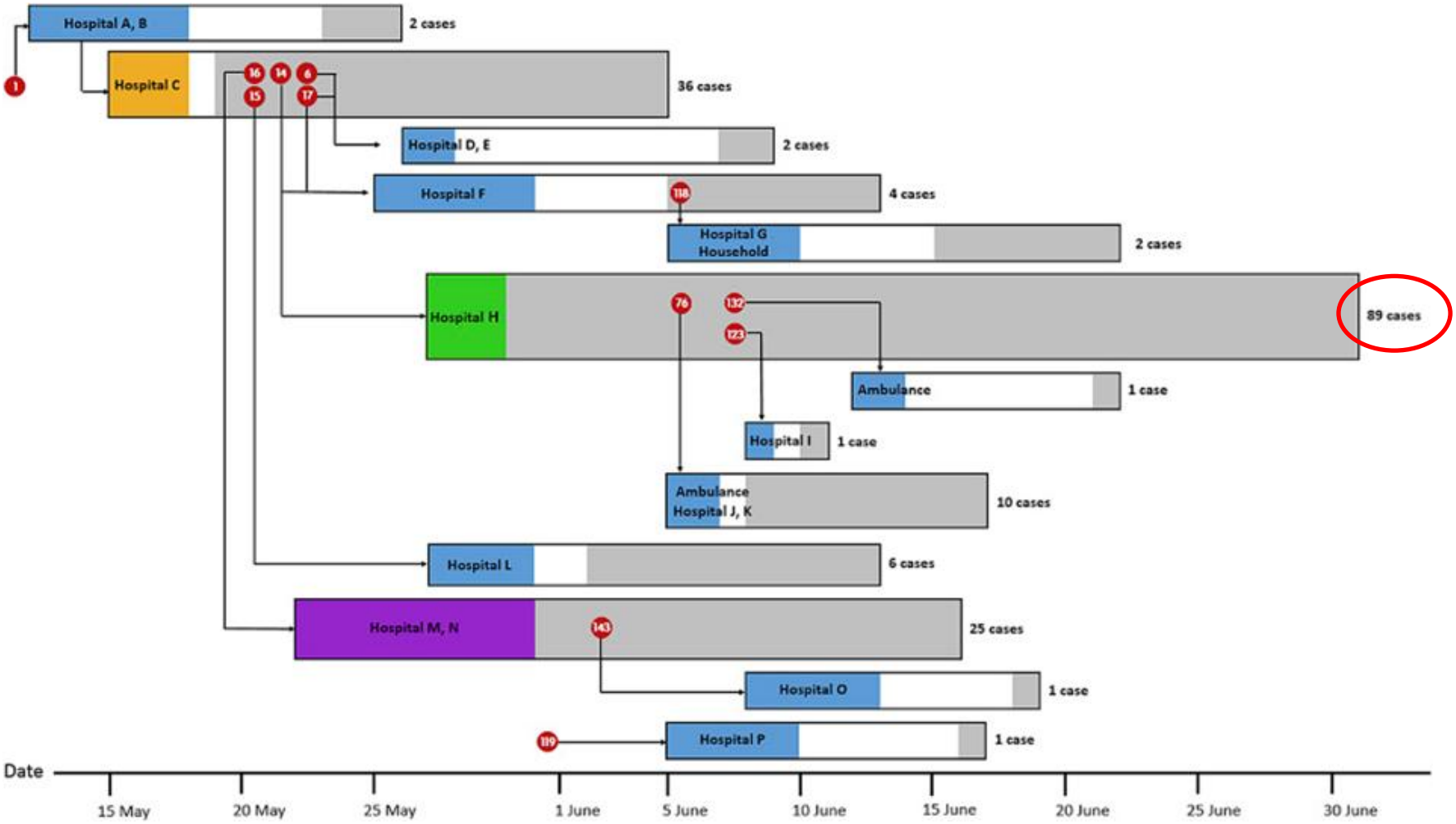
www.who.int

Link to Health Care Facilities



KCDC. *Osong Public Res Perspect 2015 6(4), 219-223*

Link to Health Care Facilities



KCDC. *Osong Public Res Perspect 2015 6(4), 269-278*

Healthcare-associated spread

Characteristics	No. of patients
Known setting of contact, n(%)	
Health care facility	178(98.0)
Household	1(0.5)
Ambulance	3(1.5)
Health care worker - no. (%)	
Yes	**38 (20.4)**
No	148 (79.6)

KCDC. ***Osong Public Res Perspect 2015 6(4), 219-223***

Source of Exposure	No. of Patients (%)
Admission to a health care facility for treatment	37 (34)
Outpatient visit to a health care facility for treatment	68 (62)
Emergency department	8(8)
Outpatient facility	42(42)
Visit to a patient at a health care facility	18 (17)
Potential case contact not related to exposure at a health care facility	26 (24)
Contact with a patient with a confirmed MERS-CoV infection	22 (20)
Contact with a person with a severe respiratory illness of unknown	4 (4)

Types of Secondary Exposure to MERS-CoV in 109 Patients
Patients may have had more than one type of exposure.

Ikwo k. et. al. NEJM 2015;372:846-54

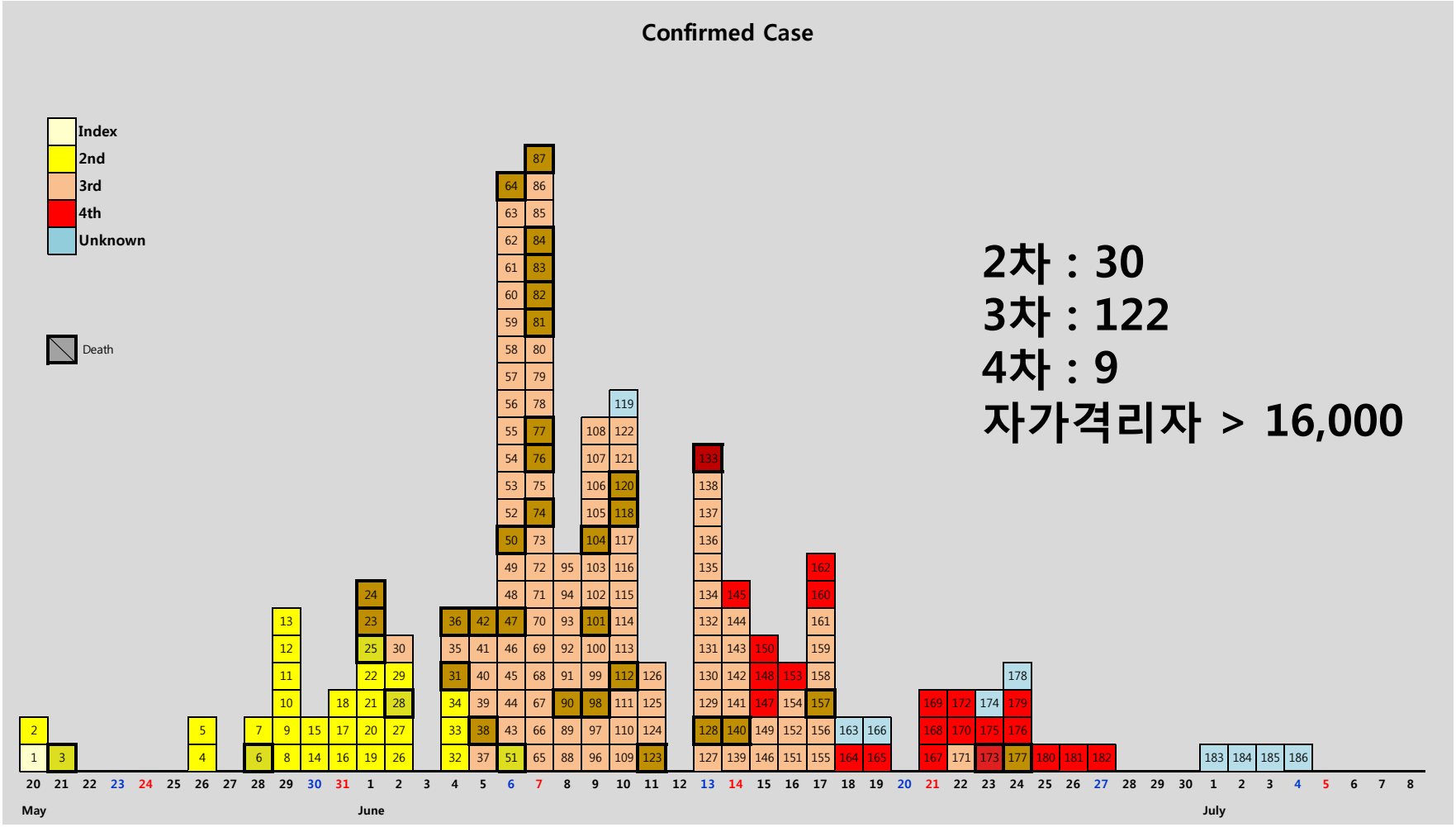
Healthcare-associated spread

Infection source	Healthcare worker with infected				
	Subtotal	Doctor	Nurse	Care giver	Other
No. 1 (M/68 yr)	5	1	4	-	-
No. 6 (M/71 yr)	1	-	-	-	1
No. 14 (M/35 yr)	9	3	3	1	2
No. 15 (M/35 yr)	2	-	1	1	-
No. 16 (M/40 yr)	7	-	-	6	1
No. 36 (M/82 yr)	1	-	1	-	-
No. 75 (F/63 yr), no. 80 (M/35 yr)	1	-	1	-	-
No. 76 (F/75 yr)	5	1	-	1	3
No. 119 (M/35 yr)	1	-	1	-	-
No. 132 (M/55 yr)	1	-	1	-	-
No. 135 (M/33 yr)	3	2	-	-	1
Total	36	7	12	9	8

Others : 방사선사, 청원경찰, 안전요원, 응급실 이송요원, 구급요원, 구급차 운전자, 의료기관의 정보통신업체 근로자.

SG Kim et al. ***Korean Med Assoc 2015 July; 58(7): 647-654***

2015 MERS in Korea



Clinical presentation

	No. fo patient(%)
Fever/chills	138 (74.2)
myalgia	47 (25.3)
cough	33 (17.7)
Gastric symptom (Nasea/vomiting/diarreha)	24 (12.9)
headache	16 (8.6)
sputum	14 (7.5)
Sore throat	8 (4.3)

	MERS	SARS
Fever (>38°C)	98%	99–100%
Chills or rigors	87%	15–73%
Cough	83%	62–100%
Dry	56%	29–75%
Productive	44%	4–29%
Haemoptysis	17%	0–1%
Headache	11%	20–56%
Myalgia	32%	45–61%
Shortness of breath	72%	40–42%
Nausea	21%	20–35%
Vomiting Diarrhoea	21% 26%	20–35% 20–25%
Sore throat	14%	13–25%
Rhinorrhoea	6%	2–24%

KCDC. *Osong Public Res Perspect 2015 6(4), 219-223*
Alimuddin et. al. Lancet 2015 386(9997), 995-1007

Clinical presentation

Symptoms during the disease course - no./total no. (%)†	
Fever	177/186 (95.2)
Cough	142/184 (77.2)
Sputum	121/184 (65.8)
Myalgia	118/184 (60.3)
Diarrhea	**95/184 (51.6)**
Dyspnea	85/184 (46.2)
Nausea or vomiting	76/184 (41.3)
Headache	74/184 (40.2)
Sore throat	33/184 (17.9)
Decreased consciousness	32/184 (17.4)
Abdominal pain	30/184 (16.3)
Hemoptysis	24/184 (13.0)
Rhinorrhea	9/184 (4.9)
Rash	5/184 (2.7)
Asymptomatic	2/186 (1.1)

Chest radiologic finding - no./total no. (%)††	
Abnormal finding at admission	123/180 (68.3)
Abnormal finding during the disease course	149/180 (82.8)
Resolution of abnormal finding at discharge	54/149 (36.2)

Superspreader

83.2% of the transmission events were linked : 156/186

Patient number	1	14	15	16	76
Infectedno.ofpatients	28	85	6	23	11
Age(y)	68	35	35	41	75
Sex	Male	Male	Male	Male	Female
Bodymassindex	27	30	24	24	19
Underlyingdisease	Hypertension, asthma	No	No	Familialadenomatous polyposis	Diabetesmellitus, multiplemyeloma
Exposedduration(d)*	10	9	10	11	2
Exposedsetting	GW(27cases) OPD(1case)	ER(78cases) GW(4cases) Other(3cases)	GW(6cases)	GW(22cases) Other(1case)	ER(4cases) GW(3cases) Other(4cases)
Number of close contact	626	594	304	277	805
Personal protective equipment	No	Intermittent	No	No	No
Pneumonia	Present	Present	Present	Present	Present
Cough	Frequent	Frequent	Rare	Frequent	Rare
Prognosis	Survived	Survived	Survived	Survived	Expired
Aerosol-generating procedure	No	No	No	No	No

KCDC. *Osong Public Res Perspect 2015 6(4), 269-278*

Treatment

Variable	Value
Antiviral agents - no./total no.(%)	137/184 (74.5)
Interferon + Ribavirin + Lopinavir/ritonavir	112/137 (81.8)
Interferon + Ribavirin	15/137 (10.9)
Ribavirin + Lopinavir/ritonavir	7/137 (5.1)
Ribavirin mono	2/137 (1.5)
Lopinavir/ritonavir mono	1/137 (0.7)
Antibiotics - no./total no.(%)	138/184 (75.0)
Mechanical ventilation - no./total no.(%)	45/184 (24.5)
Hemodialysis - no./total no.(%)	15/184 (8.2)
Extracorporeal membrane oxygenation - no./total no.(%)	13/184 (7.1)
Convalescent serum - no./total no.(%)	7/184 (3.8)
Intravenous immunoglobulin - no./total no.(%)	5/184 (2.7)

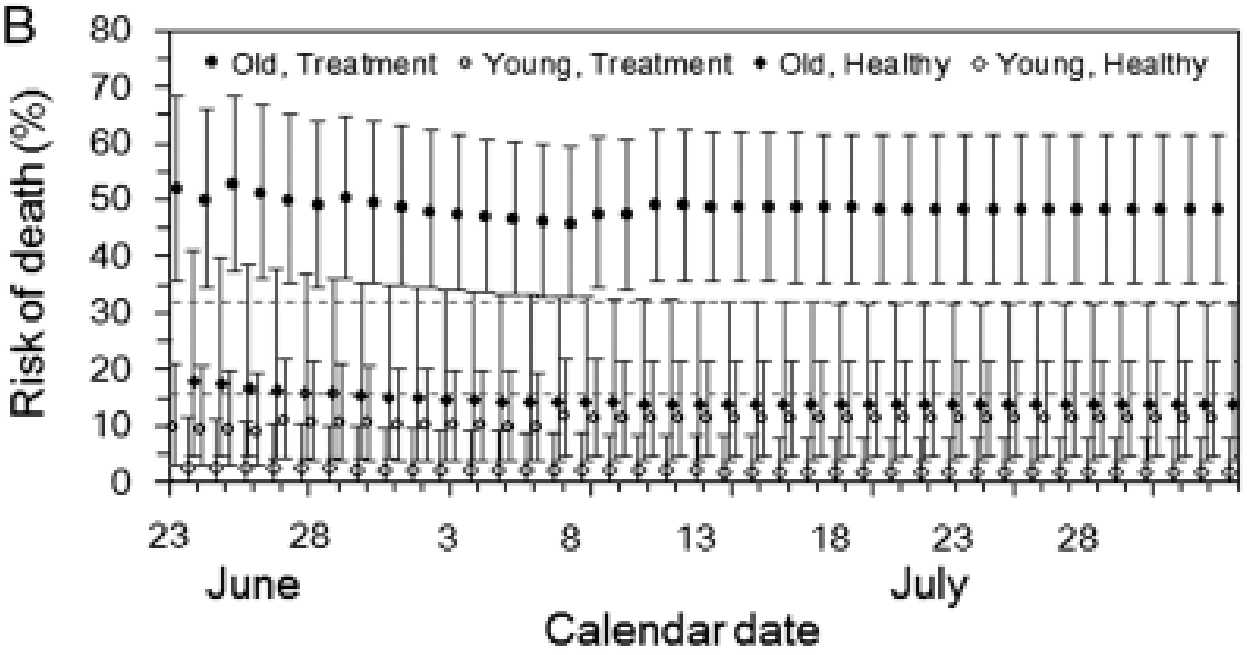
Mortality

Reporting country	Cases(n)	Death(n)	Ratea(%)
Saudi Arabia	1250	536	42.9
Republic of Korea	186	36	19.9
United Arab Emirates	81	11	13.5
Jordan	34	12	35.3
Qatar	13	5	38.5
Cumulative number	1610	620	38.5

기준 : 2012 - 2015.10.1, 유럽질병통계청ECDC

Risk of Death
MERS in KOREA

Variables	Univariate odds ratio(95 %CI)	Pvalue
Age (≥60 years old)	9.3 (5.3–16.9)	<0.01
Sex (female to male)	1.3 (0.8–2.1)	0.57
Patients under treatment	7.8 (4.0–16.7)	<0.01



Mizumoto et al. *BMC Medicine (2015) 13:228*

Survivor and Non-survivals

Characteristics	Survivors (N=150)	Non-survivors (N=36)	P Value
Median age (IQR) - years	51 (39-62)	69 (61-76)	<0.01
Age >55 years - no. (%)	64 (42.7)	33 (91.7)	<0.01
Healthcare workers - no. (%)	37 (24.7)	1 (2.8)	0.02
Symptoms during the whole disease course			
Dyspnea	50/148 (33.8)	35/36 (97.2)	<0.01
Headache	65/148 (43.9)	9/36 (25.0)	0.04
Decreased consciousness	12/148 (8.1)	20/36 (55.6)	<0.01
One or more coexisting medical condition - no. (%)	**73 (48.7)**	**30 (83.3)**	<0.01
Hypertension	40 (26.7)	19 (52.8)	<0.01
Diabetes mellitus	23 (15.3)	12 (33.3)	0.01
Solid organ malignancy	14 (9.3)	11 (30.6)	<0.01
Chronic heart disease	9 (6.0)	8 (22.2)	<0.01
Chronic lung disease	6 (4.0)	13 (36.1)	<0.01
Vital sign at admission - no./total no. (%)			
Systolic blood pressure <90 mmHg	3/148 (2.0)	4/36 (11.1)	0.03
Respiratory rate >20 /min	29/148 (19.6)	18/36 (50.0)	<0.01

Survivor and Non-survivals

Characteristics	Survivors (N=150)	Non-survivors (N=36)	P Value
Laboratory abnormalities at admission – no./total no. (%)			
White blood cell count >10,000 /uL	3/140 (2.1)	5/36 (13.9)	0.01
White blood cell count <4,000 /uL	65/140 (46.4)	10.36 (27.8)	0.04
Platelet <150,000 /uL	60/140 (42.9)	22/36 (61.1)	<0.01
Serum albumin <3.5 g/dL	40/130 (30.8)	21/35 (60.0)	<0.01
Serum creatinine >1.5 mg/dL	3/136 (2.2)	7/35 (20.0)	<0.01
C-reactive protein >3 mg/dL	56/134 (41.8)	22/32 (68.8)	<0.01
PaO2:FiO2 ratio <300	11/25 (44.0)	14/19 (73.7)	0.05
Treatment - no./total no. (%)			
Mechanical ventilator	17/148 (11.5)	28/36 (77.8)	<0.01
Hemodialysis	3/148 (2.0)	12/36 (33.3)	<0.01
Antibiotics	104/148 (70.3)	34/36 (94.4)	<0.01

Risk Factors for Death from MERS

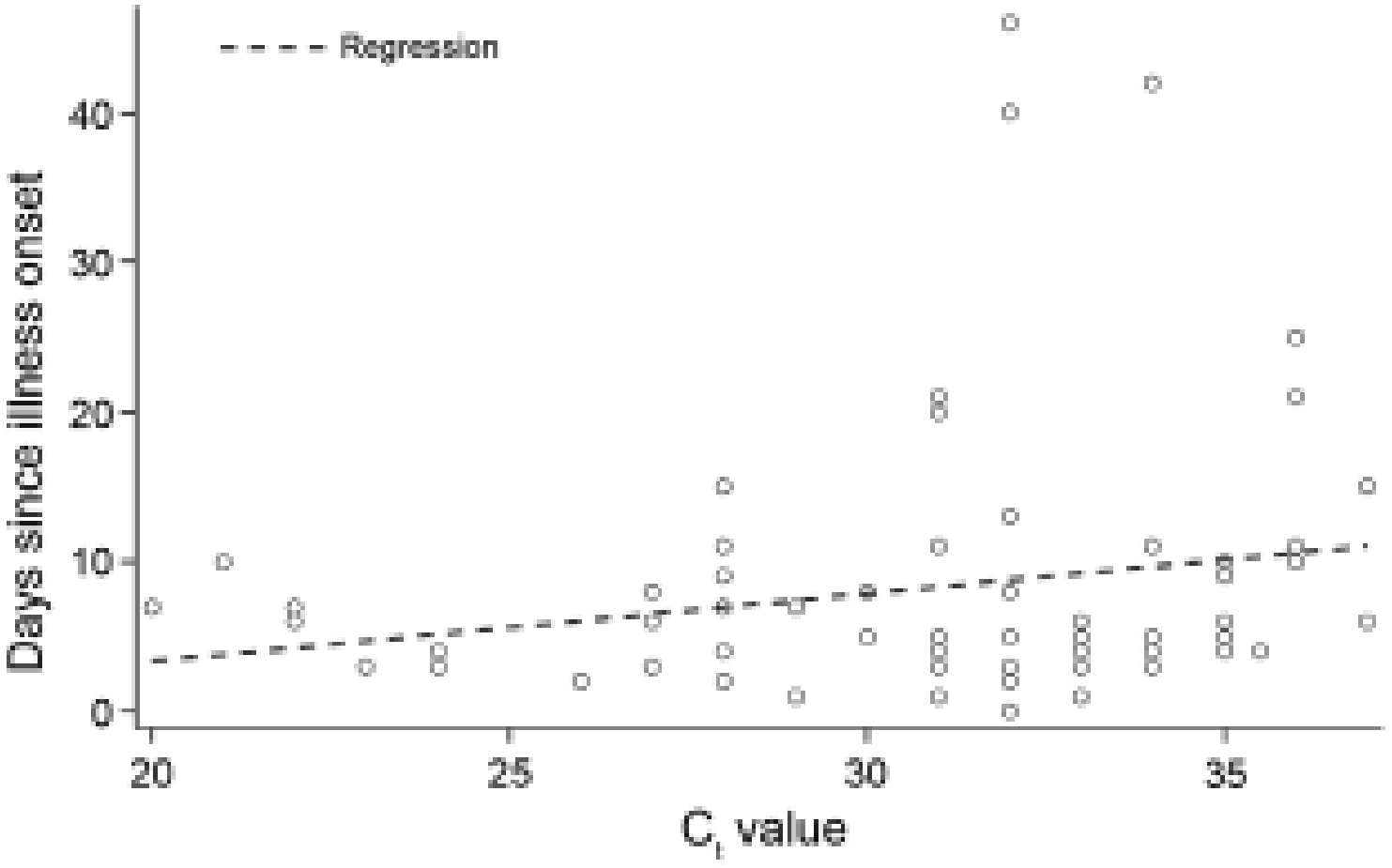
Variable	Odd ratio (95% CI)†	P value
Age ≥55 years	8.63 (3.19-23.30)	<0.01
Symptoms during the whole disease course		
Dyspnea	18.81 (2.39-148.41)	<0.01
Coexisting medical condition		
Diabetes	2.47 (1.06-5.72)	0.04
Chronic lung disease	2.24 (1.04-4.79)	0.04
Vital sign at admission		
Systolic blood pressure <90 mmHg	5.38 (1.65-17.49)	<0.01
Laboratory abnormalities at admission		
White blood cell count >10,000 /uL	3.16 (1.10-9.07)	0.03
Treatment		
Mechanical ventilation	8.04 (2.95-21.92)	<0.01

***In Cox-regression analysis, the data was censored at September 30, 2015 for survivors**

Survivors and Non-survivors (Mechanical Ventilation)

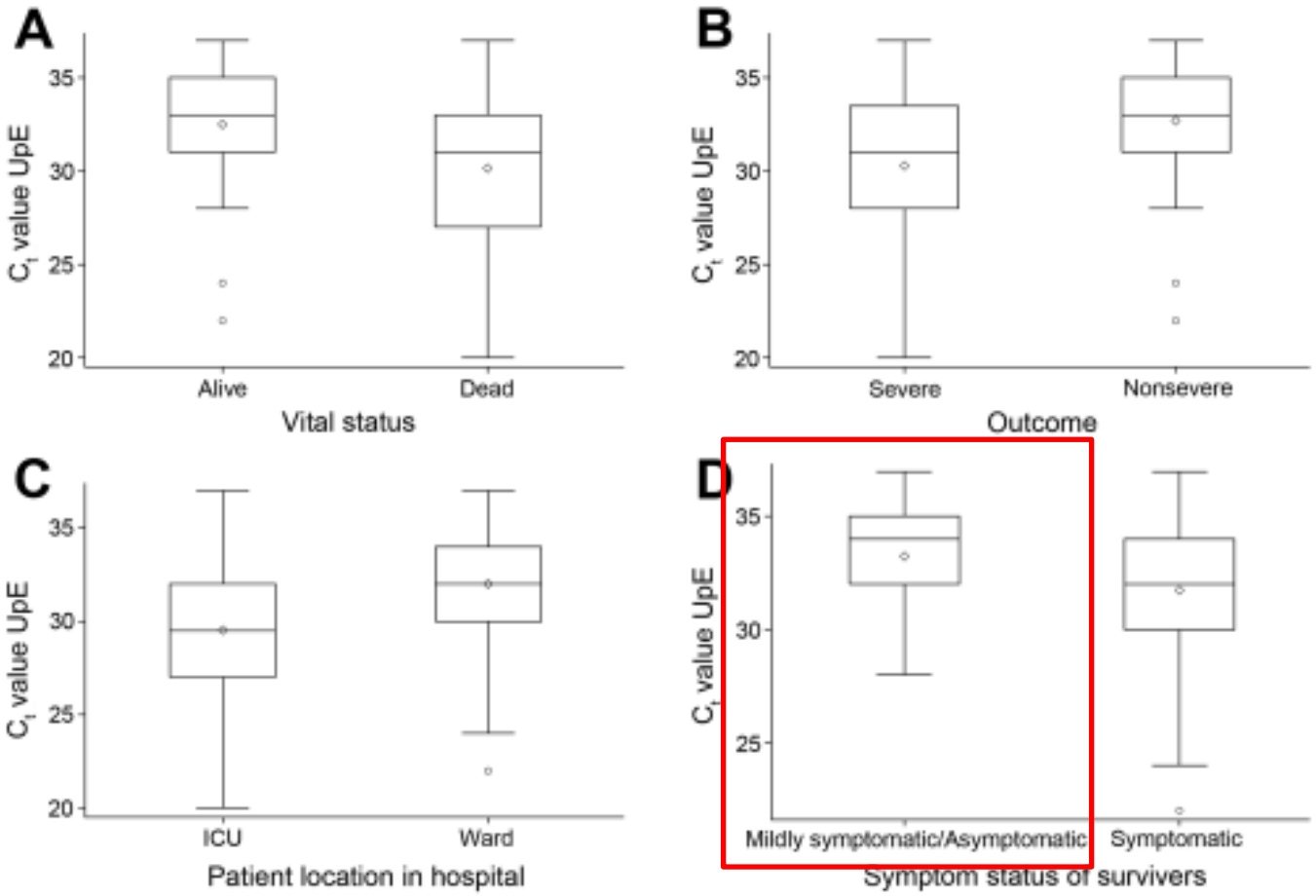
Characteristics	Survivors (N=17)	Non-survivors (N=28)	P Value
Median age (IQR) - years	55 (36-66)	67 (59-74)	<0.01
Age ≥55 years - no. (%)	9 (52.9)	26 (92.9)	<0.01
Healthcare workers - no. (%)	5 (29.4)	1 (3.6)	0.02
Symptoms during the whole disease course			
Diarrhea - no. (%)	13 (76.5)	13 (46.4)	0.05
One or more coexisting medical condition - no. (%)	6 (35.3)	21 (75.0)	<0.01
Chronic lung disease	0 (0)	11 (39.3)	<0.01
Solid organ malignancy	0 (0)	7 (25.0)	0.03
Laboratory abnormalities during the whole disease course - no. (%)			
Alanine aminotransferase >45 IU/L	16 (94.1)	18 (64.3)	0.03
Serum creatinine >1.5 mg/dL	3 (17.6)	14 (50.0)	0.03
Treatment - no. (%)			
Extracorporeal membrane oxygenation	8 (47.1)	5 (17.9)	0.05
Convalescent serum	6 (35.5)	1 (3.6)	<0.01

Early onset and Viarl road



Daniel R et al. *Emerg Infect Dis. 2015 21(11), 269-278*

MERS-CoV Viral load



Daniel R et al. *Emerg Infect Dis. 2015 21(11), 269-278*

MERS in 3 Persons, South Korea, 2015

	Patient 1 (index patient)			Patient 2†			Patient 3‡		
Date	Days after illness onset	upE, C_t	ORF1a, C_t	Days after illness onset	upE, C_t	ORF1a, C_t	Days after illness onset	upE, C_t	ORF1a, C_t
May 20	9	18.61	19.32	2	26.23	26.63	1	28.10	28.65
May 22	11	25.24	25.67	5	35.53	35.10	3	24.67	25.04
May 25	14	26.48	27.99	11	25.20	26.10	5	26.37	25.53
May 28	17	31.23	32.05	14	32.58	34.80	8	ND	35.94
May 31	20	36.94	ND	17	ND	ND	11	26.30	28.01
Jun 4	24	ND	36.27	18	ND	ND	14	ND	ND
Jun 6	26	33.92	36.70	19	Discharged		15	Died	
Jun 8	29	36.50	ND						
Jun 9	30	36.90	37.46						
Jun 12	33	ND	ND						
Jun15	36	ND	ND						
Jun 16	37	35.46	ND						
Jun 17	38	ND	ND						
Jun 22	43	ND	ND						
Jun 23	44	32.97	36.31						
Jun 26	47	ND	ND						
Jun 29	50	ND	ND						
Jun 30	51	ND	ND						

*C_t, cycle threshold; ND, not detected; ORF1a, open reading frame 1a gene; upE, upstream envelope protein gene. Blank cells indicate not applicable.
†Wife of index patient.
‡Shared hospital room with index patient.

Jeong-Sun Yang et al. *Emerg Infect Dis. 2015 21(11), 2084-87*

Asymptomatic or subclinical

Characteristic	Health Care Worker						
	1	2	3	4	5	6	7
Age (yr)	42	29	46	39	59	28	56
Sex	Female	Female	Female	Female	Female	Female	Female
Result of chest radiography	Normal	Normal	Normal	Normal	Normal	Normal	Normal
MERS-CoV PCR test	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Viral load (Ct value)	33	37	38	34	35	30	37
Coexisting condition Diabetes mellitus	Yes	**No**	No	**No**	No	No	No
Other	No	**No**	No	**No**	No	No	No
Symptoms Feverish feeling	Yes	**No**	Yes	**No**	No	Yes	Yes
Fever, measured	Yes	**No**	No	**No**	No	No	No
Cough	Yes	**No**	No	**No**	No	No	Yes
Sore throat	Yes	**No**	Yes	**No**	No	Yes	Yes
Runny nose	No	**No**	Yes	**No**	Yes	Yes	Yes
Muscle aches	Yes	**No**	Yes	**No**	No	No	Yes
History of exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes

more than 3000 people have been screened
seven health care workers with MERS-CoV infection (two of whom were asymptomatic and five of whom had mild upper respiratory tract symptoms)through screening of single sample nasopharyngeal swabs

Ziad A. Memish et. al. ***NEJM 2013;369:884-6***

Asymptomatic

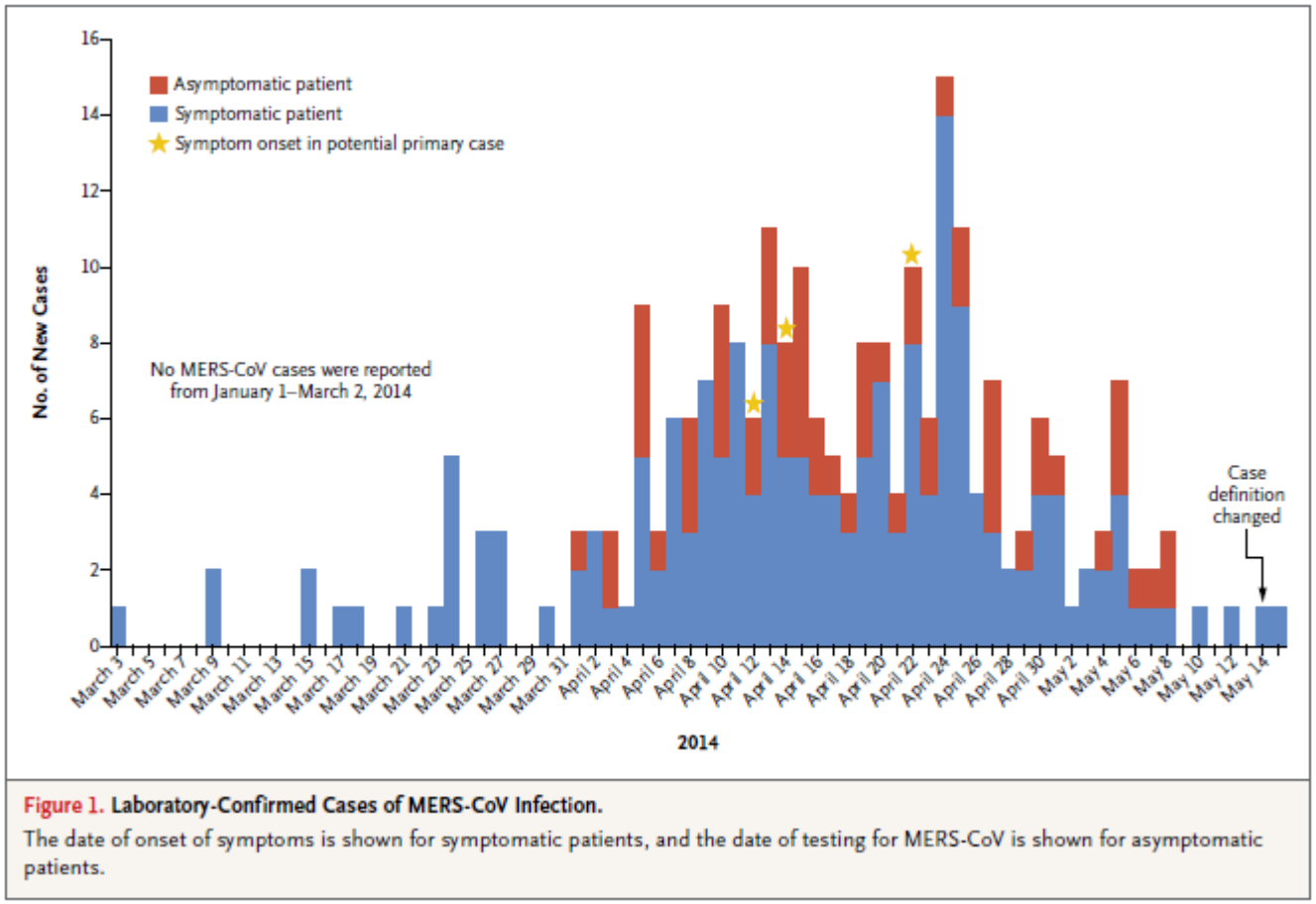


Figure 1. Laboratory-Confirmed Cases of MERS-CoV Infection.
The date of onset of symptoms is shown for symptomatic patients, and the date of testing for MERS-CoV is shown for asymptomatic patients.

Of 255 patients with laboratory-confirmed MERS-CoV infection, 93 died (case fatality rate, 36.5%). The median age of all patients was 45 years (interquartile range,30 to 59), and 174 patients (68.2%) were male. **A total of 64 patients (25.1%) were reported to be asymptomatic.**

Ikwo k. et. al. NEJM 2015;372:846-54

Middle East respiratory syndrome coronavirus antibodies

	Year of sampling	Total number	rELISA positive		Stage 1 seropositive		Stage 2 seropositive	
			n (%; 95% CI)	p	n (%; 95% CI)	p	n (%; 95% CI)	p
General population	2012–13	10 009	152 (1·5%; 1·3–1·8)	NA	17 (0·2%; 0·1–0·3)	NA	15 (0·2%; 0·1–0·2)	NA
Camel shepherds	2014	87	6 (6·9%; 2·8–13·8)	p=0·0003	2 (2·3%; 0·3–7·4)	p=0·0009	2 (2·3%; 0·3–7·4)	p=0·0004
Slaughterhouse workers	2013	140	6 (4·3%; 1·8–8·7)	p=0·0224	5 (3·6%; 1·3–7·7)	p<0·0001	5 (3·6%; 1·3–7·7)	p<0·0001

Marcel *et al.Lancet Infect Dis 2015; 15: 559–64*

Exposure type, cohort	**Country**	**Serum samples tested by**		
			$PRNT_{90}$, no. positive/no. tested†	
		S1 assay, no. positive/no. tested	S1-positive	S1-negative
Dromedary contact		20/294	10/20	1/35
A1, camel slaughterers	Qatar	**4/5**	2/4 (40, 20)	NT
A2, sheep slaughterers (contact with camels/camel slaughterers)	Qatar	**3/104**	2/3 (20, 20)	1/16 (20)
B, central animal market workers	Qatar	**1/8**	0	NT
C, barn workers at international camel racing track	Qatar	**4/22**	3/4 (40, 40, 20)	NT
D, camel farm workers	Qatar	**8/155**	3/8 (40, 40, 20)	0/19
No dromedary contact		**0/204**	NA	0/48
E, construction workers	Qatar	**0/56**	NA	0/48
F, sheep farmers	Qatar	**0/10**	NA	NT

Chantal B.E.M. Reusken. *Emerging Infectious Diseases Vol. 21, No. 8, August 2015*

Severe pnuemonia with ARDS

	MERS	SARS
Overall CFR	40%	9·6%
CFR in patients with comorbidities	60%	46%
Time from onset to ventilatory support	**Median 7 days**	Mean 11 days
Time from onset to death	**Median 11·5 days**	Mean 23·7 days
Incubation period		
Mean (95% CI; days)	5·2 (1·9–14·7)	4·6 (3·8–5·8)
Range (days)	2–13	2–14
Serial interval	7·6 days	8·4 days
Comorbidities	76%	10–30%

Alimuddin et. al. ***Lancet 2015 386(9997), 995-1007***

Time from onset to ventilatory support(n=10)	**8.4(4-14) days**
Time from onset to death(n=5)	**12.5(10-15) days**

NMC data

Time from symptom onset to death in days, median (IQR)	**15 (10-20) days**

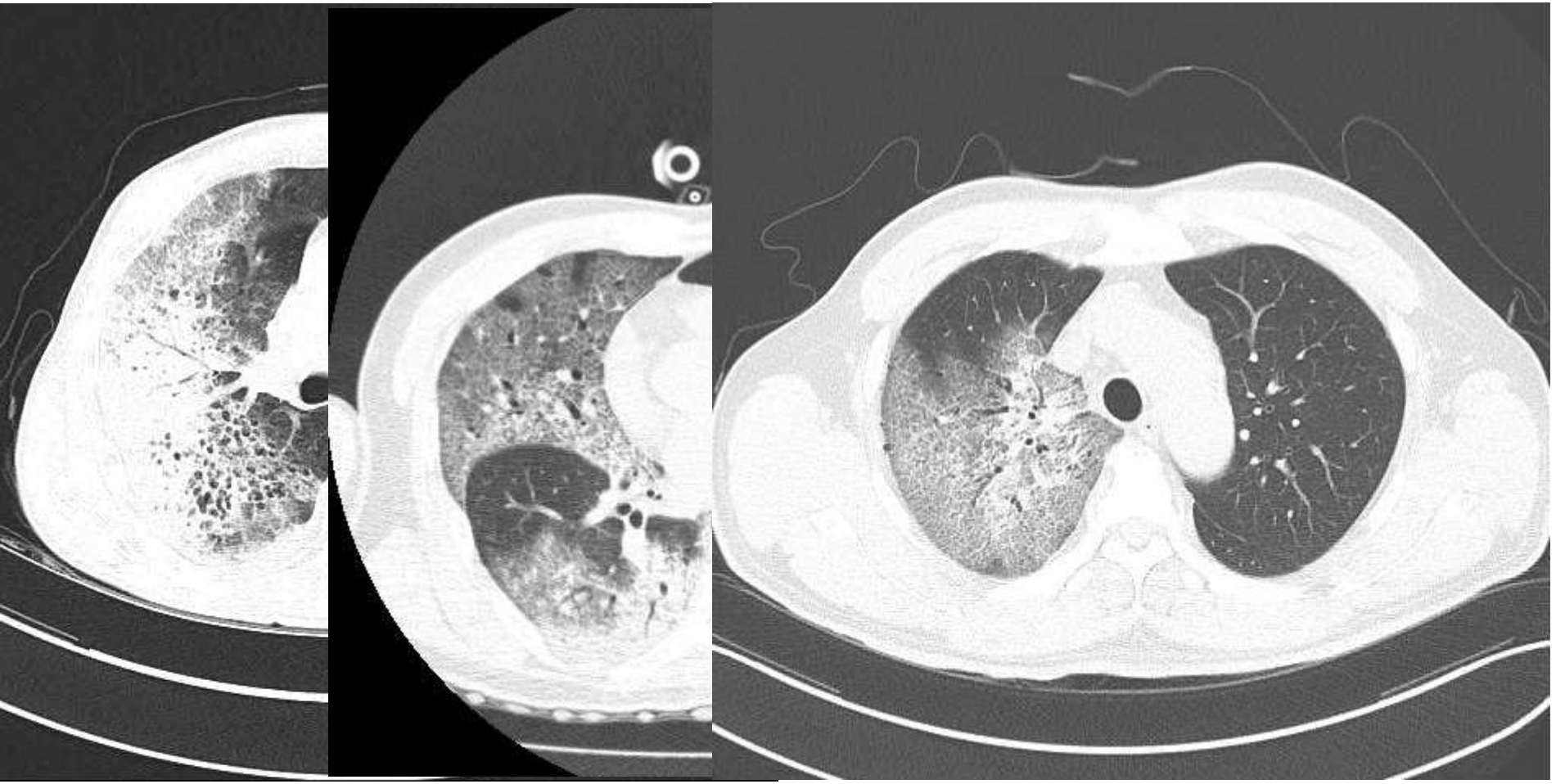
KCDC. ***Osong Public Res Perspect 2015 6(4), 219-223***

Radiologic imaging

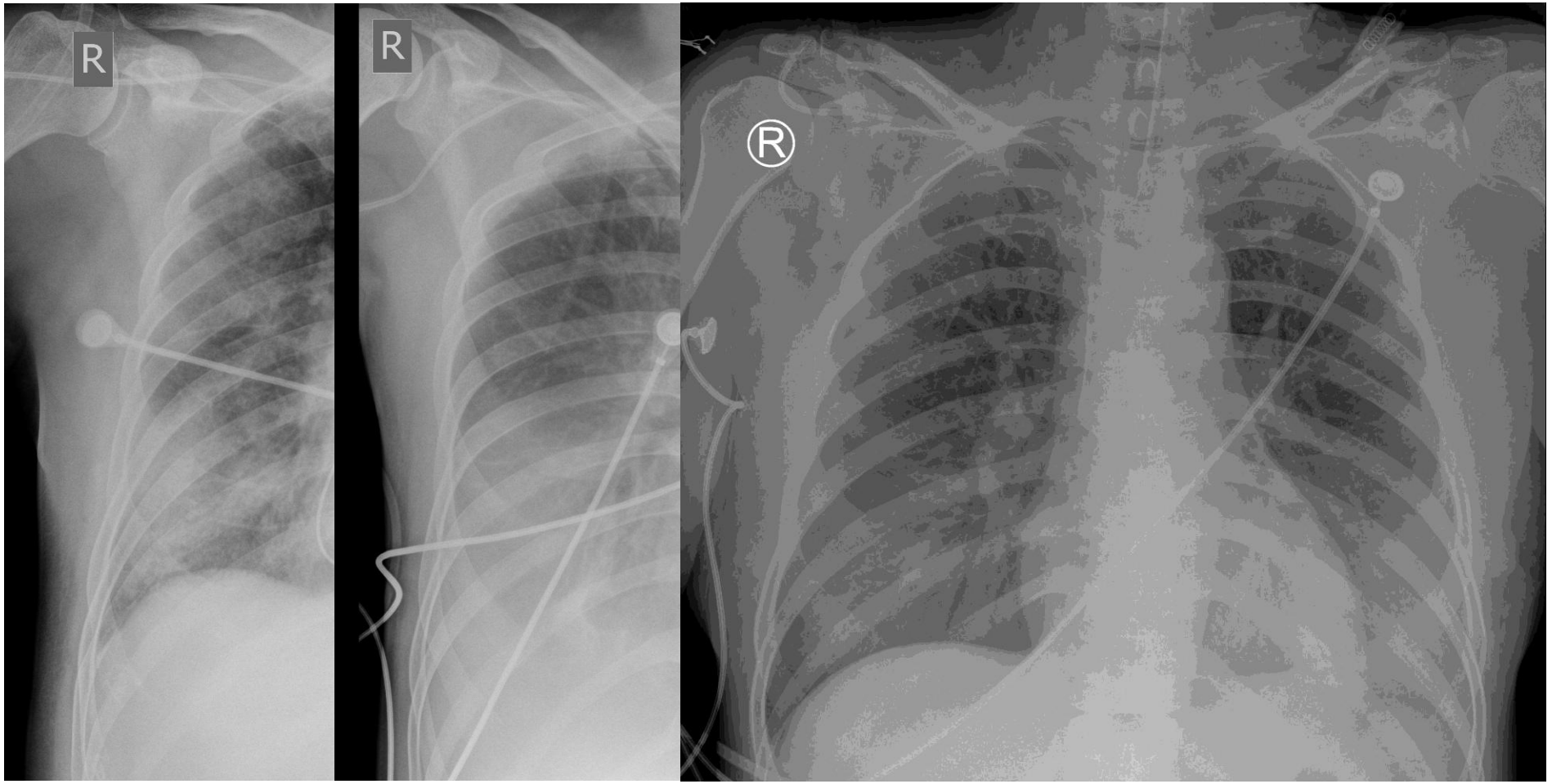
Chest radiologic finding - no./total no. (%)	
Abnormal finding at admission	118/174 (67.8)
Abnormal finding during the whole course of disease	144/174 (82.8)
Consolidation	52/144 (36.1)
Ground glass opacity (GGO)	50/144 (34.7)
Consolidation + GGO	15/144 (10.4)
Consolidation + GGO + Pleural effusion	5/144 (3.5)
Consolidation + GGO + Cavitation	3/144 (2.1)
Consolidation + Pleural effusion	3/144 (2.1)
Cavitation	2/144 (1.4)
Others	14/144 (9.7)
Resolution of abnormal finding at discharge	51/144 (35.4)

Ailan et al. *AJR 2014; 203:782–787*

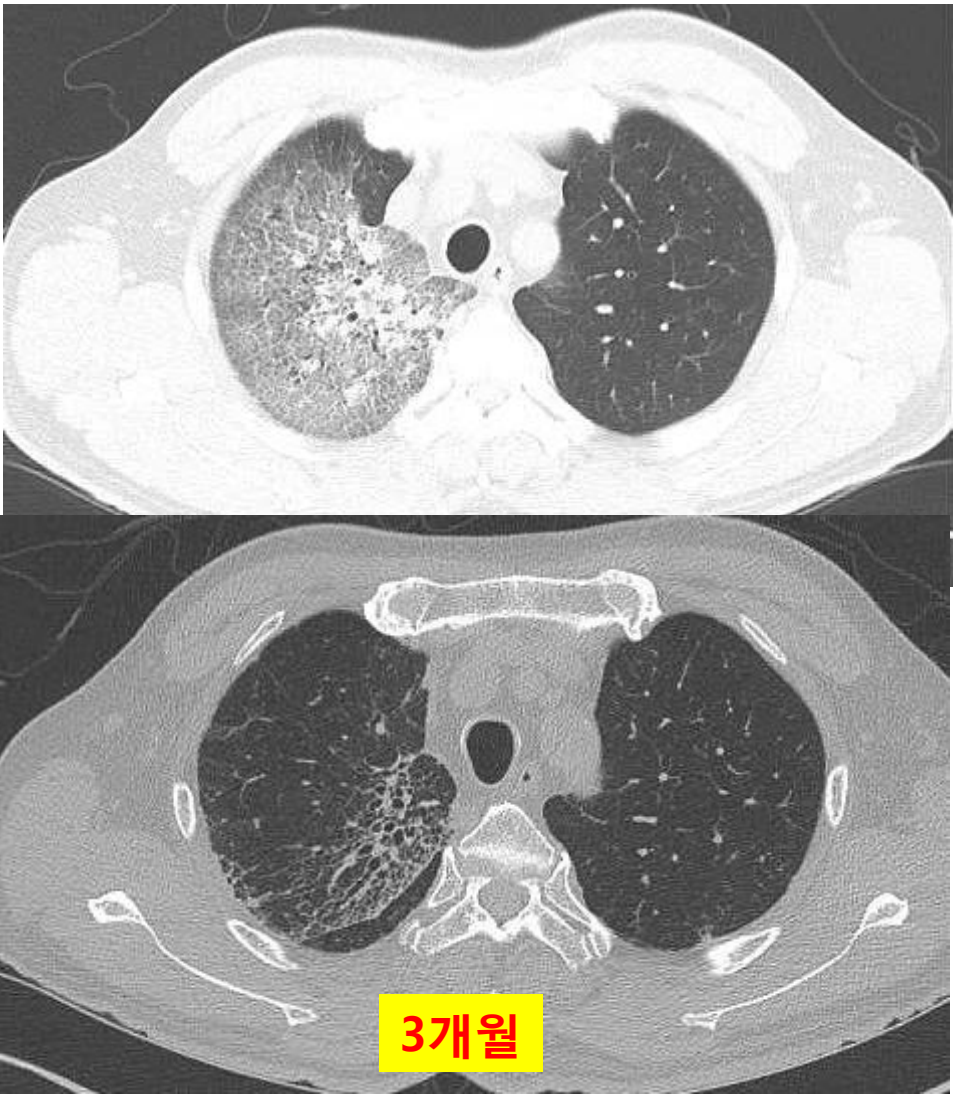
CT imaging(initaial)

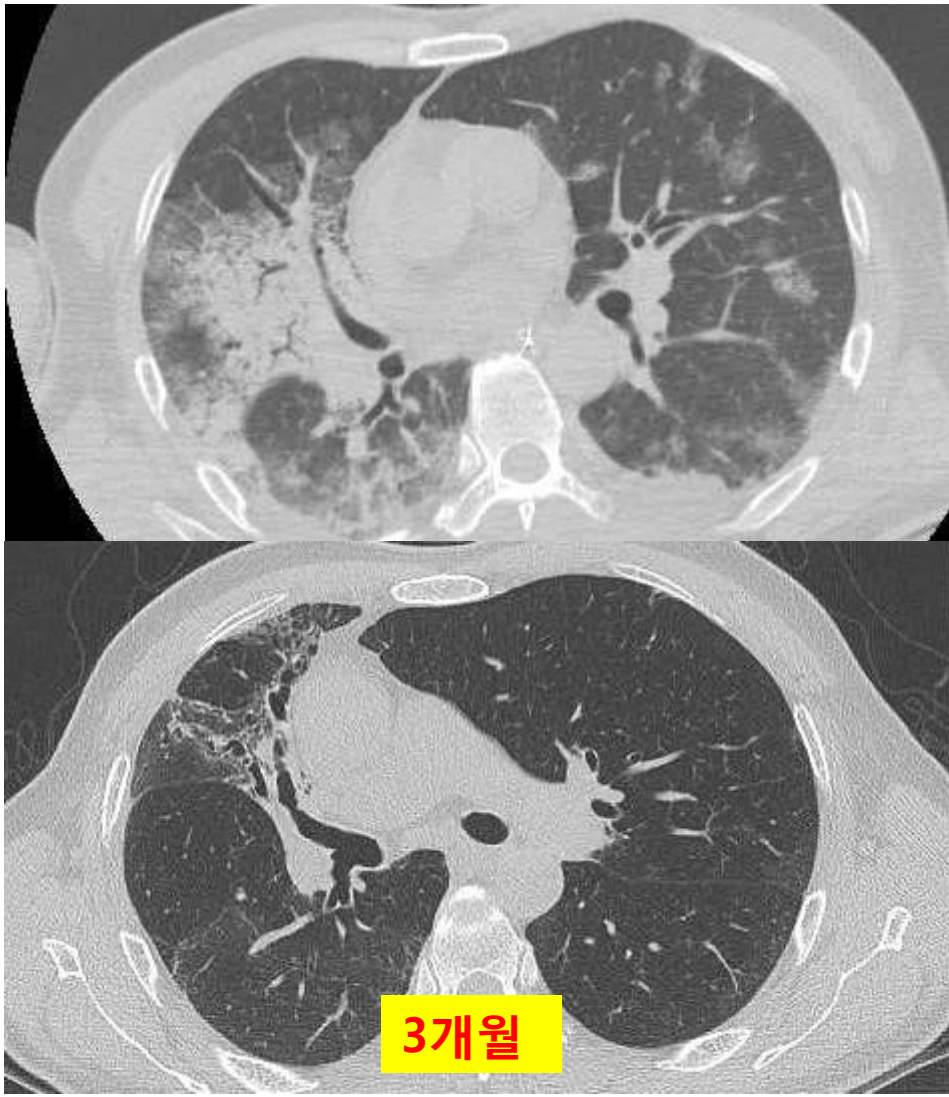


Relatively radiolucent when intubation



Chronic fibrosis





3개월

3개월

Anti-viral Treatment

① MERS-CoV 감염이 확진된 환자에게는 조기에 항바이러스제 치료를 고려한다.

② 증상이 있는 MERS-CoV 감염 의심 환자에게도 조기에 항바이러스제 치료를 고려한다

③ MERS-CoV 감염 의심 환자에서 폐렴의 다른 원인병원체가 확인되거나 유전자검사(RT-PCR) 결과가 48시간 간격으로 음성인 경우 항바이러스제 치료 중단을 고려한다.

④ 폐렴이 동반된 환자에서는 MERS-CoV 감염이 의심되어도 일반적인 폐렴 가능성을 고려하여 가능한 한 빨리 적절한 경험적 항생제를 투여해야 한다. 이후 검사 결과에 따라 항생제를 조정해야 한다.

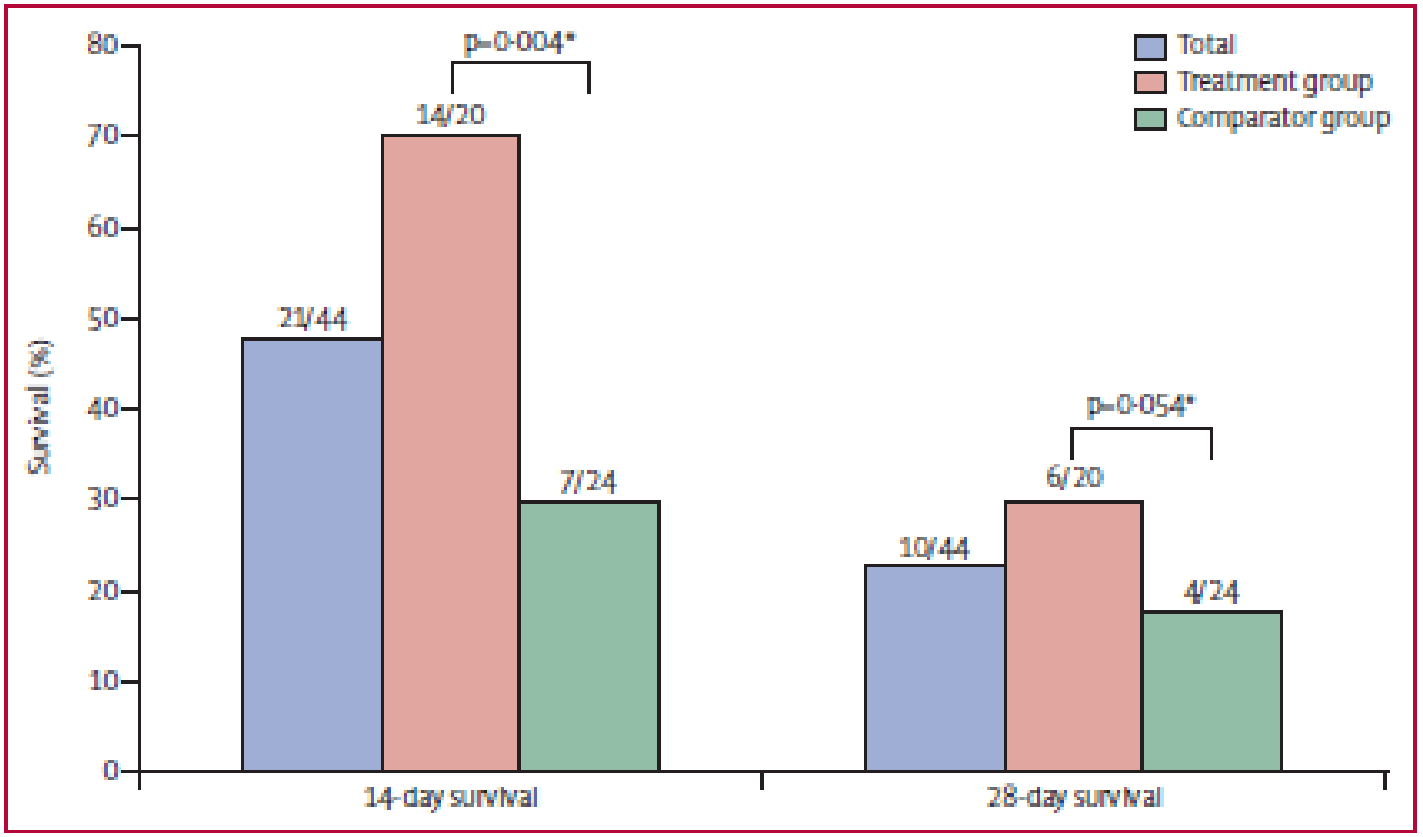
⑤ 항바이러스제 치료로 ribavirin + interferon α2a + lopinavir/ritonavir 병합요법을 권한다 (표 1).

⑥ 항바이러스제는 10-14일 투여를 권하지만 환자 상태에 따라 결정해야 한다.

⑦ MERS 환자에서 고용량 스테로이드 사용은 권하지 않는다.

MERS 항바이러스제 진료지침,2015.06.12

Ribavirin and pegylated interferon alfa-2a therapy

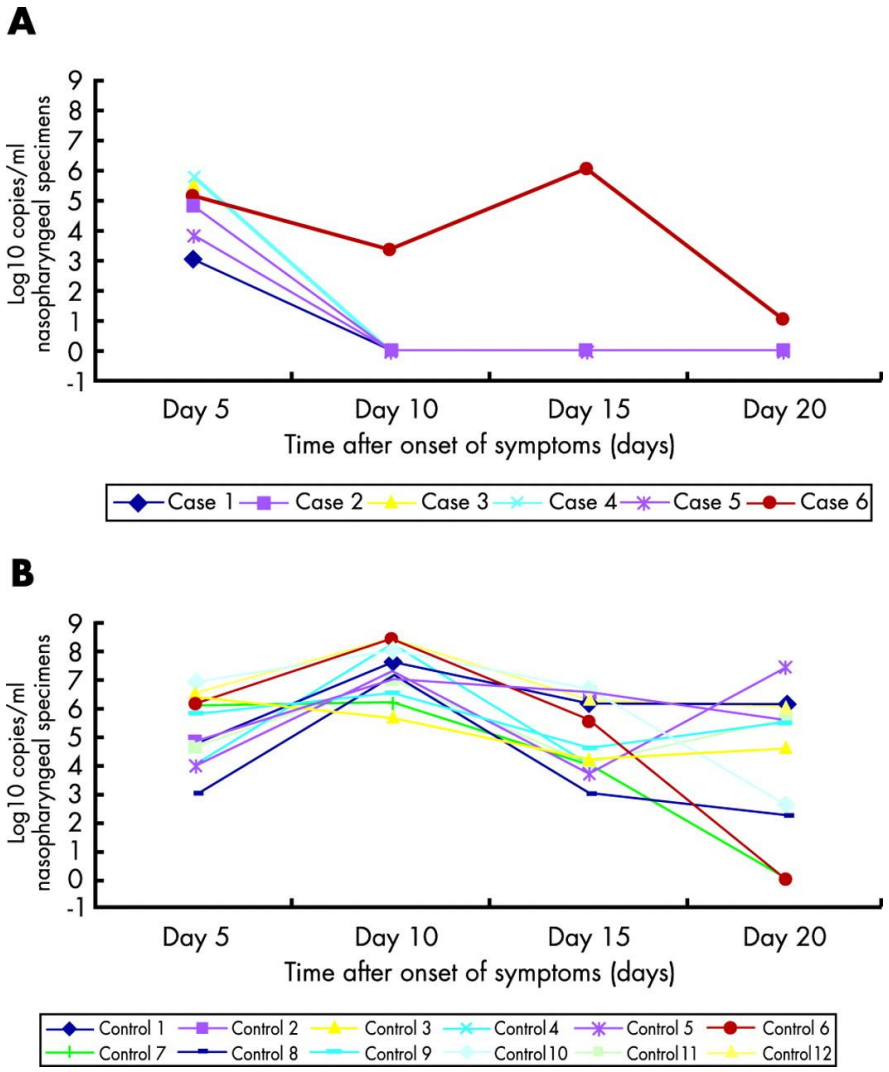


Ali S Omrani et. al. Lancet Infect Dis 2014;14:1090-95

lopinavir/ritonavir in the treatment of SARS

(A) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of six patients in the initial treatment subgroup. Note that case 6 was given pulse methylprednisolone on day 7.

(B) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of 12 patients in the historical control group.



Ali S Omrani et. al. Lancet Infect Dis 2014;14:1090-95

Convalescent Plasma

	Plasma group[a]	Steroid group[b]	p
Discharge rate by day 22 following onset of illness	73.4% (n = 14)	19% (n = 4)	0.001
Discharge rate by day 22 after adjustment for co-morbidities	77.8% (14/18)	23% (3/13)	0.004
Death rate	0%	23.8% (n = 5)	0.049

Comparison of treatment outcome between patients in the plasma-treated and steroid-treated groups
[a]Three doses of methylprednisolone, followed by convalescent plasma.
[b]Four or more doses of methylprednisolone.

Soo YO et al. Clin Mircobiol infect 2004;10:676-8

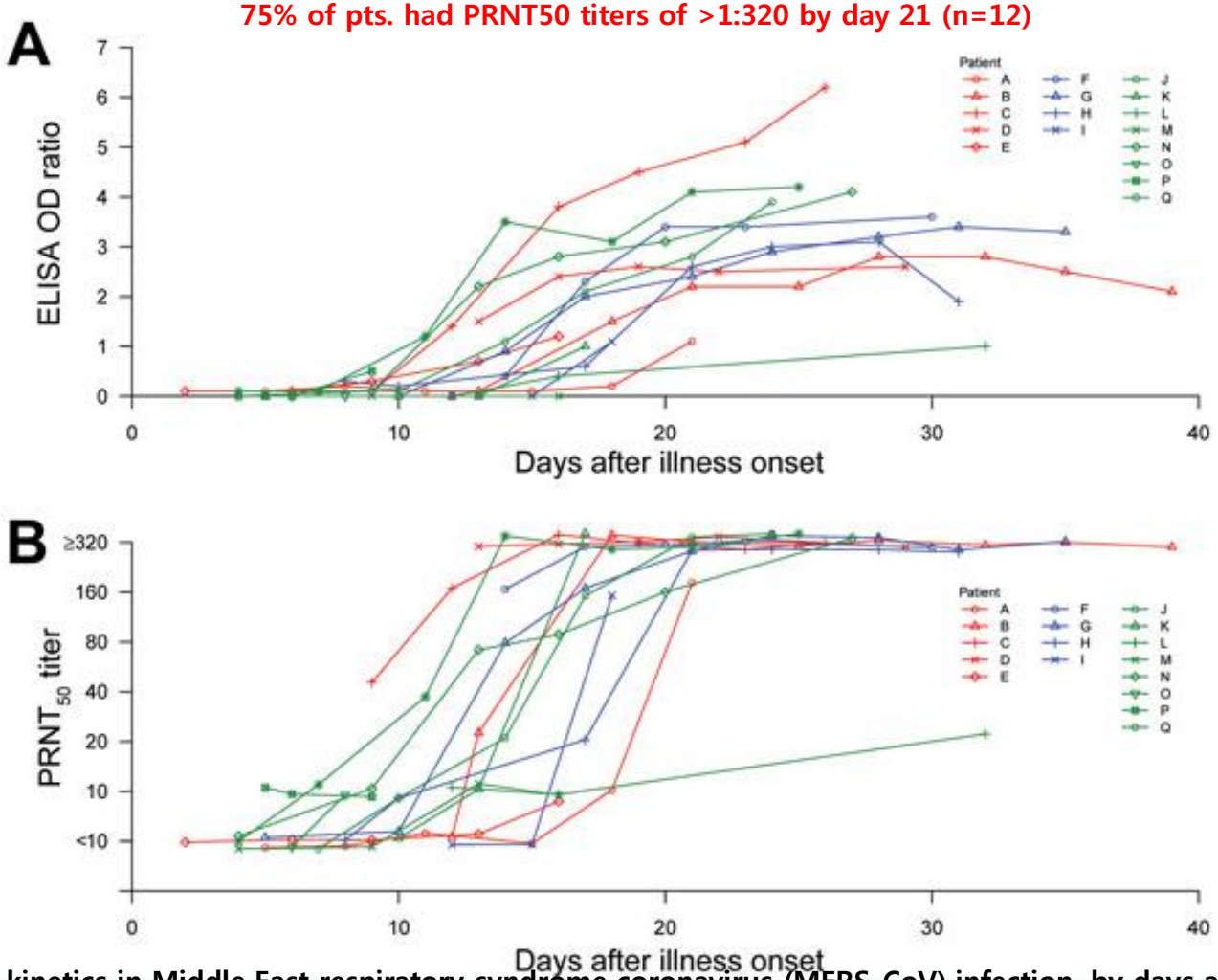
Characteristic	**Good outcome[a]**	**Poor outcome[b]**	**P value**	**Logistic regression P value**
No. of patients	33	47		
Age	37.9±12.5	50.2±15.1	<0.001	0.009
Admission LDH (IU/l)	268.6±117.6	334±183.7	0.08	0.014
Mean day of plasma infusion[c]	**11.7±2.3**	**16.0±6.0**	**<0.001**	**0.012**
Mean plasma volume	253.6±99.9	297.23±141.4	0.11	0.174
PCR positive and seronegative for SARS[d]	20	10	<0.001	0.006

Comparison of clinical characteristics of patients with SARS according to outcome
[a]Discharged by day 22 from symptom onset
[c]Calculated from day of symptom onset
[c]Death before day 22 or late Discharge
[d]Status at time plasma was given

Cheng Y. et al. ***Eur J Clin Mircobiol infect disease 2005;24:44-6***

Antibody kinetics

75% of pts. had PRNT50 titers of >1:320 by day 21 (n=12)



Antibody response kinetics in Middle East respiratory syndrome coronavirus (MERS-CoV) infection, by days after illness onset, as determined by using a 50% endpoint plaque reduction neutralization test (PRNT50) (A) and an S1 IgG ELISA (B). Red indicates patients with severe illness requiring mechanical ventilation; green indicates patients with severe illness requiring only supplemental oxygen therapy; and blue indicates

Park WB et al. *Emerg Infect Dis 2015 Dec*

Multidisplinary apporach

Factors contributed to spread

- A lack of awareness about MERS
- Prolonged duration of exposure before dx
- Proper isolation
- Suboptimal IPC(Infection prevention and control)
- Crowded emergency and multibed rooms : (Inadequate ventilation)
- The practice of "doctor shopping"
- The custom of having many family members or other visitors in patient's room

KCDC. ***Osong Public Res Perspect 2015 6(4), 219-223***

MERS 2015

- Noble HID can be disaster.
  - Ongoing threat to health and livelihood of people everywhere
  - Gross domestic product 0.3%↓, >135,000 tourists canceled the visit
  - >2,700 schools were closed, >16,000 people uncedwent house quarantine.
- MERS : Asymptomatic to servere disease
  - Rapid progression
  - Asymptomatic person could be the source of infection
- Diagnosis
  - X-ray may help in predicting MERS-CoV positivity, progression
  - A direct and safe access to a BLS 3,4 lab
- Multidisplinary apporach ; specifically trained HCWs
  - Infectious Diseases specialist and intensivist, respirology, cardiology, surgery, psychiatry, radiology, laboratory

Gaps in our knowledge

- Modes of infections
  - Potential source of infection in the community
- Natural histroy : risk factor for the severity
- Diagnosis
  - Cycle threshold
- Treatment
  - A specific antiviral therapy
  - Convalescent plasma, Ventilator, ECMO
- Host response :
  - cytokine response
  - serosurvey data,
- Virus : Genetic variation
- Surveillance system
  - Case-finding
  - Outbreak management