

Organ failure scores in neonatal sepsis.

Hugo Devlieger, member PDCO



Classical end-point: all-cause short term (28d.) mortality

Neonatal sepsis has low mortality: large study population needed:

- Cohen-Wolkewiez et al. 2009: near term EOS: total 1,3% mortality but 19,1% in Gram neg. Sepsis. LOS: 0,4% mortality but 24% in Gram neg.
- Choice of 28 days is arbitrary and may be too short
- Attributing death to sepsis as opposed to the underlying disease is difficult
- > Withdrawal of intensive care clouds mortality as an end-point
 - End-of-life decision preceded death in 95% in Dutch NICU (Verhagen et al. 2009)



Organ dysfunction scores ?

As the magnitude of organ dysfunction is a key element in defining the severity of sepsis, this should be reflected in the endpoints

- The interaction between sepsis and multiple organ failure is only poorly defined in children (Leclerc et al. 2005)
- Degree of organ dysfunction and the number of failing organs differ in the individual patient over time often independently of the course of the infection
- No distinction is possible between the course of the disease and the impact of treatment.



Organ dysfunction scores ?

- In the newborn infant patterns of organ dysfunction can be identified which correspond to the severity of the sepsis.
- Hence "time to organ dysfunction resolution" can be derived as a single alternative end point to mortality

All organ dysfunction scores are not equal

- Prognostic scores aim to describe the severity of illness based on co-morbidities, and/or some physiological disturbance at baseline of groups of critically ill patients and to derive the mortality or morbidity risk of the newborn: (SNAP, SNAPPE, SNAPH, SNAPPEH, CRIB II, NTISS etc.)
 - single shot scores are not intended to assess day-by-day evolution of morbidity as a result of therapy
 - > do not provide detail on disease progression or response to treatment
 - > Do not include perinatal items as PPROM, APGAR, etc.
 - Partial risk adjustment in observational studies
 - Validation of the randomization
 - Stratification of patients at entry in a RC trial
 - Selection by means of severity index the group of patient for which
 - there is the greatest chance to demonstrate a treatment effect



Outcome score in neonatal care

- Describes the severity of illness based on specific organ dysfunction and failure due to sepsis on a day-by-day base
- Requirements of reliable score in sepsis to be used as a surrogate for disability-free survival and basis for validation as defined by Tarnow-Modi (2005):
 - 1) a causal connection should exist between change in the score and change in disability-free survival
 - 2) the score fully captures all the effects of treatment on "disability-free survival".

Neonatal Multiple Organ Dysfunction Score (Janota J et al. 2001)

- Developed in 142 VLBW infants (<31w GA and<1500g BW)</p>
- Daily scoring of seven organ systems (CNS, cardiovascular, renal, respiratory gastrointestinal, haemocoagulation and acidbase status.
- Scoring up to 28 days after birth



Central nervous system (expressed as a presence of intraventricular hemorrhage or leukomalacia)

Hemocoagulation balance (expressed as platelet count) Respiratory system (expressed as a need for ventilation support)

Gastrointestinal system (expressed as a mode of nutrition and presence of inflammatory or surgical bowel complication)

Cardiovascular system (expressed as ability to keep adequate arterial blood pressure in normovolemic patient)

Renal function (expressed as urine output)

Acid-base balance (expressed as maximum base deficit) Intraparenchymal blood or development of overt hydrocephalus, leukomalacia with cyst formation, or cerebral atrophy with large ventricles Platelet count below 30 × 10⁹/L

2

Mechanical ventilation in intubated patient

Signs of necrotizing enterocolitis or perforation of the gut (laboratory, clinical, X-ray, and ultrasound) or ileostomy, colostomy, drainage, or T-tube present Adequate blood pressure has not been attained despite pharmacological support

Urine output below 0.2 mL/kg/h, or peritoneal dialysis, hemodialysis, or hemofiltration Maximum base deficit over 15 mEq/L Blood in one or both ventricles

Platelet count within a range of 30–100 × 10⁹/L Ventilation status requiring continuous positive airway pressure, or fraction of inspired oxygen over 0.21 (arterial hemoglobin oxygen saturation of 88%–95%) in spontaneously breathing patient

Total parenteral nutrition

Continuous pharmacological support to keep adequate blood pressure

Urine output within the range of 0.2-1 mL/kg/h

Maximum base deficit within a range of 7 up to 15 mEq/L

No hemorrhage or subependymal germinal matrix hemorrhage only

0

Platelet count over 100 x 109/L

Spontaneous respiration without ventilation support (arterial hemoglobin oxygen saturation of 88%–95%)

Enteral feeding or combination of enteral and parenteral nutrition

Adequate blood pressure: mean arterial blood pressure within the normal range established by Bada (17) during first 48 h and by Tan (18) during 28 days Urine output over 1 mL/kg/h

Maximum base deficit up to 7 mEq/L

NEOMOD score









Neomod score



Comment on the NEOMOD score

- Designed as a predictive score but can be used as a one-off score as a daily or as a Delta score
- ➤ Can not be applied for term and preterm infants ≥ 1500g
- > The CNS criteria are specific for the VLBW infant
- Liver dysfunction is not included in the score while it is an important target in neonatal sepsis



Adaptations to the NEOMOD score

- Adapted CNS score: ex. Sarnat score or other
 Liver dysfunction: cholestatic icterus should be included
- Other organ dysfunction?

Alternatives:

Sequential Organ Failure Score

- Time to recovery of organ failure
- > New organ failure
- Organ failure–free days (from enrolment to 28 days) e.g Activated Prot C trial
- "free days"
 - Ventilator free days, vaso-active drugs free days

Adaptation of the paediatric scores

- MODS score
- PELOD score
- P-MODS score

Table 1. Organ dysfunction criteria

Cardiovascular dysfunction Despite administration of isotonic intravenous fluid bolus 240 mL/kg in 1 hr • Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age OR • Need for vasoactive drug to maintain BP in normal range (dopamine $>5 \mu g/kg/min$ or dobutamine, epinephrine, or norepinephrine at any dose) OR Two of the following Unexplained metabolic acidosis: base deficit >5.0 mEg/L Increased arterial lactate >2 times upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 secs Core to peripheral temperature gap >3°C Respiratorv^a • PaO₂/FIO₂ <300 in absence of cyanotic heart disease or preexisting lung disease OR • PaCO₂ >65 torr or 20 mm Hg over baseline PaCO₂ OR Proven need^b or >50% FIO₂ to maintain saturation ≥92% OR Need for nonelective invasive or noninvasive mechanical ventilation^c Neurologic Glasgow Coma Score ≤11 (57) OR Acute change in mental status with a decrease in Glasgow Coma Score >3 points from abnormal baseline Haematologic Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients) OR International normalized ratio >2 Renal Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine Hepatic Total bilirubin ≥4 mg/dL (not applicable for newborn) OR ALT 2 times upper limit of normal for age BP: blood pressure; ALT, alanine transaminase; ^aacute respiratory distress syndrome must include a PaO₂/FIO₂ ratio

BP: blood pressure; AL1, alanine transaminase; "acute respiratory distress syndrome must include a PaO_2/FIO_2 ratio $\leq 200 \text{ mm Hg}$, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO_2/FIO_2 ratio must be $\leq 300 \text{ mm Hg}$; ^bproven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; ^cin postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated. *Source: Goldstein B et al. 2005*



PELOD score

Cardiovascular dysfunction

- Despite administration of isotonic intravenous fluid bolus \geq 40 mL/kg in 1 hr
- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age OR
- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

 Two of the following Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate >2 times upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 secs Core to peripheral temperature gap >3℃

Respiratory failure

Respiratory^a

 PaO₂/FIO₂ <300 in absence of cyanotic heart disease or preexisting lung disease OR

OR

OR

- PaCO₂ >65 torr or 20 mm Hg over baseline PaCO₂
- Proven need^b or >50% FIO₂ to maintain saturation \ge 92%
- Need for nonelective invasive or noninvasive mechanical ventilation^c

Neurologic

- Glasgow Coma Score ≤11 (57)
- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

OR

Haematologic

- Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
 OR
- International normalized ratio >2

Renal

● Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

• Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

• ALT 2 times upper limit of normal for age

P-MODS

Score	0	1	2	3	4
Lactic acid, mmol/L	<1	1–2	2–5	5-7.5	>7.5
Pao ₂ /Fio ₂	>150	150 - 100	100-75	75-50	$<\!\!50$
Bilirubin ^a					
µmol/L	<8.5	8.5-34.2	34.2-85.5	85.5-171	>171
mg/dL	< 0.5	0.5 - 2.0	2.0 - 5.0	5.0 - 10.0	> 10
Fibrinogen ^b					
µmol/L	>4.40	4.40-3.70	3.70 - 3.0	3.0 - 2.20	$<\!\!2.20$
mg/dL	>150	150 - 125	125-100	100 - 75	<75
BUN ^c					
µmol/L	< 7.10	7.10-14.3	14.3 - 21.4	21.4 - 28.5	>28.5
mg/dL	$<\!\!20$	20-40	40-60	60-80	>80

Alternatives:

Severity of illness score originally designed as predictive scores can be sequentially assessed as for example the NTISS. This reflects, however mainly the treatment received by the infant and is not accurate as a surrogate endpoint as it is based on the assumption that therapeutic intensity is a direct correlate of illness severity.



Conclusions

- The only published outcome score in neonatal care is too limited to apply to all newborn infants
- > The score has never been applied in a RT
- Adapted paediatric scores may be useful in neonatal trials
- Scores are not addressing organ dysfunction in the specific condition of sepsis although sepsis is the major cause of organ dysfunction in the NICU as well as in the PICU

CRIB

CRIB (Clinical Risk Index for Babies)

Birthweight (g)	Gestation (wk)	Congenital malformation (excluding inevitably lethal malformation)
<pre>C > 1350 C 851-1350 C 701-850 C < or = 700</pre>	C > 24 C < or = 24	None Not acutely life-threatening Acutely life-threatening
Maximal Base Excess in first 12 h (mmol/L)	Minimum appropriate FIO ₂ in first 12 h (TcPO2 or PaO2 = 6.7-10.7 kPa or SaO2 = 88-95%)	Maximum appropriate FIO ₂ in first 12 h (TcPO2 or PaO2 = 6.7-10.7 kPa or SaO2 = 88-95%)
C >-7	C <= 0.4	○ <= 0.4
C - 7 to - 9.9	0.41 - 0.60	0.41 - 0.80
C - 10 to -14.9	C 0.61 - 0.90	C 0.81 - 0.90
C < or = - 15	C 0.91 - 1.00	0.91 - 1.00

Total CRIB points

Measure during the first 12 h. Infants of birthweight 1550 g or less or gestational age less than 31 weeks.

Ref : The International Neonatal Network. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. Lancet 1993;342 : 193-98

CRIB II

Variables	Values	Points (help)
Gestation (weeks)	Male infants	F
Birthweight (g) (enter the value)	0 Enter	0
Contation (unake)	Female infants	
Sestation (weeks)		0
Birthweight (g) (enter the value)	0 Enter	
Temperature at admission (°C)	-	0
Base excess (mmol/L)	-	0
	Predicted Death Rate : 0	Total CRIB II score : 0
Compute		Total CRIB II score = Sum (noints)
Clear	Predicted death rate = $e^{\text{Logit}}/(1+e^{\text{Logit}})$	The range of possible CRIB II score is 0 to 27

CRIB II



CRIB II (Clinical Risk Index for Babies)



Reference

. G. Parry et al. CRIB II : an update of the Clinical Risk Index for Babies score. Lancet 2003;361(9371):1789-91

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		N	lale	e int	fant	s							-	Fe	ma	le ii	ofar	ats		-	-	-	_
2751 to 3000											0	2751 to 3000											0
2501 to 2750										1	0	2501 to 3000						-			-	1	6
2251 to 2500									3	0	0	2001 to 2700	H				-	⊢			2		6
2001 to 2250									2	0	0	2201 to 2000	H		H		\vdash	⊢			1	0	6
1751 to 2000								3	1	0	0	1751 to 2000	H	\vdash	\vdash	-	⊢	⊢		3	1	0	6
1501 to 1750						6	5	3	2	1	0	1501 to 1750			\vdash	⊢	⊢	6	4	3	1	0	6
1251 to 1500					8	6	5	3	3	2	1	1351 to 1500			H	⊢	7	5	4	3	2	1	1
1001 to 1250		12	10	9	8	7	6	5	4	3	3	1001 to 1350		11	10	8	7	6	5	4	3	3	1
751 to 1000		12	11	10	8	7	7	6	6	6	6	751 to 1000			10	0	8	7	6	5	5	5	5
501 to 750		12	12		10	•	8			8		501 to 750	13	12	11	10	9	8	8	7	7	7	ř
		13	12		10	°	Ľ	Ľ	Ů	Ľ		251 to 500	14	13	12	11	11	10	10		ŕ	ŕ-	⊢
251 to 500	15	14	13	12	11	10	10					20110 000	22	23	24	25	26	27	28	29	30	31	32
	22	23	24	25	26	27	28	29	30	31	32		**	23	24	20	20	41	20	2.0	50	1.	0.

Birthweight (g) and gestation (weeks)

<= 29.6 5	
29.7 to 31.2 4	< -26 7
31.3 to 32.8 3	-26 to -23 6
32.9 to 34.4 2	-22 to -18 5
34.5 to 36 1	-17 to -13 4
36.1 to 37.5 0	-12 to -8 3
37.6 to 39.1 1	-7 to -3 2
39.2 to 40.7 2	-2 to 2 1
>=40.8 3	>= 3 0

NTISS

A.F. M.F.	-		yes			volume expansion (+- to mong)			100	
fechanical ventilation ^a	3	C	yes	C	no	Volume expansion (>15 mL/kg) ^c	3	C	yes	no
fechanical ventilation with muscle elaxation ^a	4	c	yes			Vasopressor administration (1 agent) ^d	2	c	yes	c
light-frequency ventilation*	4	c	yes			Vasopressor administration (>1 agent) ^d	3	c	yes	no
Surfactant administration	1	c	yes	c	no	Cardiopulmonary resuscitation	4	c	yes	C
indotracheal intubation	2	C	yes	C	no	Pacemaker on standby®	3	C	yes	C
racheostomy care ^b	1	c	yes	~		Pacemaker used ^e	4	C	yes	no
racheostomy placement ^b	1	C	yes	2	no					
Extracorporeal membrane exygenation	4	c	yes	c	no					
Drug therapy						Monitoring				~
Intibiotic administration (<= 2 agents)	1	C	yes	c	-	Frequent vital signs	1	C	yes	no
Antibiotic administration (> 2 agents ¹	2	C	yes		110	Phiebotomy (5-10 blood draws) ^h	1	c	yes	c
Diuretic administration (enteral)®	1	c	yes			Extensive phlebotomy (> 10 blood draws) ^h	2	c	yes	no
Diuretic administration (parenteral) ^g	2	C	ves	1	no	Cardiorespiratory monitoring	1	C	yes	C
			/					25		C
Inticonvulsant therapy	1	C	yes	C	no	Thermoregulated environment	1	C	yes	no
minophylinne administration	1	c	yes	c	no	Noninvasive oxygen monitoring	1	c	yes	C no
Other unscheduled medication	1	c	yes	c	no	Arterial pressure monitoring	1	C	yes	C no
steroid administration (postnatal)	1	c	yes	C	no	Central venous pressure monitoring	1	c	yes	no
Potassium binding resin Idministration	3	c	yes	c	no	Urinary catheter	1	c	yes	no
reatment of metabolic acidosis	3	C	yes	c	no	Quantitative intake and output	1	c	yes	C no
Metabolic / nutrition						Transfusion				
Savage feeding	1	c	yes	c	no	Intravenous gamma globulin	1	c	yes	no
Phototherapy	1	c	yes	c	no	Double volume exchange transfusion	3	r	yes	no
ntravenous fat emulsion	1	c	yes	c	no	Partial volume exchange transfusion	2	c	yes	C
ntravenous amino acid solution	1	c	yes	c	no	Red blood cell transfusion (<=15 ml/kg ⁱ	2	c	yes	c
nsulin administration	2	c	yes	c	no	Red blood cell transfusion (>15 ml/kg) ⁱ	3	c	yes	no
Potassium infusion	3	C	yes	c	no	Platelet transfusion	3	C	yes	no
						White blood cell transfusion	3	C	yes	no
Procedural						Vascular access				
ransport of patient	2	c	yes	c	no	Peripheral intravenous line	1	c	yes	no
Dialysis	4	C	yes	c	no	Arterial line	2	C	yes	no
Single chest tube in place ^j	2	c	yes	c	no	Central venous line	2	C	yes	no
Aultiple chest tubes in place ¹	3	C	yes							
Thoracentesis	3	C	yes	C	no	Clear				
Pericardial tube in place	4	C	yes	C	-	Cicult				
Pericardiocentesis	4	C	yes	1	110					

CY

Minor operation ^k Major operation k

2

(yes (no C yes 4

NTISS = SUM (points for activities performed) = 0

SNAP





Mean B.P. (mmHg), minimum
Heart Rate, minimum
PaO2/ FIO2 (FIO2 in %)
Hematocrit , maximum
Immatures Ratio (help)
B.U.N.
Indirect Bilirubin
Sodium (mEq/L) minimum
Sodium (mEq/L) minimum Dotassium (mEq/L) minimum V 0
Sodium (mEq/L) minimum v 0 Potassium (mEq/L) minimum v 0 Bicarbonate (mEq/L) minimum v 0
Sodium (mEq/L) minimum ▼ 0 Potassium (mEq/L) minimum ▼ 0 Bicarbonate (mEq/L) minimum ▼ 0 Całcium (Total, max) 0
Sodium (mEq/L) minimum Potassium (mEq/L) minimum Sodium (mEq/L) minimum Bicarbonate (mEq/L) minimum Calcium (Total, max) Calcium (Total, min)

Temperature - 0 **Respiratory rate** - 0 PaCO2 (mmHg) - 0 Hematocrit, minimum - 0 Absolute neutrophils - 0 Creatinine - 0 **Direct Bilirubin** - 0 Stool Guaiac - 0 Glucose maximum - 0 Glucose minimum - 0 Serum pH - 0 SNAP =0 Clear

Perinatal Extension







Predicted death rate **Birth weight** g Compute Clear

+ (1.0898 * (1 if <5th% for gestational age, 0 if >= 5th% for gestational age) + (0.7422 * (SNAP) * (1 if SNAP <= 15, 0 if SNAP > 15)) + (0.6251 * (SNAP) * (1 if SNAP >= 16 and <=20, 0 if SNAP < 16 or > 20)) +(0.4674 * (SNAP) * (1 if SNAP >= 21 and <=27, 0 if SNAP < 21 or > 27)) + (0.4073 * (SNAP) * (1 if SNAP >= 28, 0 if SNAP < 28)) - (0.5429 * (SNAP/birthweight) * (1 if SNAP <= 15, 0 if SNAP > 15)) -(0.4088 * (SNAP/birthweight) * (1 if SNAP >= 16 and <= 20, 0 if SNAP < 16 or > 20)) -(0.2809 * (SNAP/birthweight) * (1 if SNAP >= 21 and <= 27, 0 if SNAP < 21 or > 27)) - (0.2399 * (SNAP/birthweight) * (1 if SNAP >= 28, 0 if SNAP < 28)) Predicted Death Rate= e(logit) / (1 + e(logit)) Weight at 5th% for body weight

g

=0

logit = -14.6889 +(8.6774 * (1/

(birthweight in kilograms))) +(1.4414 * (1

if Apgar at 5 minutes < 7, 0 if Apgar >= 7)





Compute

Clear weight at 5th% for body weight = -0.06217*(weeks)⁴+7.585979*(weeks)³-337.3942*(weeks)²+6583.4774*(weeks)-47312.4

Oxygenation Index



Back to SNAP-PE

EUROPEAN MEDICINES AGENCY

SNAP-II and SNAPPE II (Score for Neonatal Acute Physiology and SNAP Perinatal Extension)

SNAPP II

Variables	Values	Points
Mean Blood Pressure	E	О
Lowest temperature	-	0
P0 ₂ (mmHg) / FIO ₂ (%)	<u> </u>	0
Lowest serum pH	-	0
Multiple seizures	-	0
Urine output (mL/kg.h)	<u> </u>	Ю
SN	AP II : 0	
Apgar score	-	0
Birth weight	-	0
Small for gestational age (help)	<u> </u>	0
SNAPPE II : 0 In-hospital mortality :	see below Data are collected within NICU	the first 12 hours after admission to the

SNAP-II and SNAPPE II (Score for Neonatal Acute Physiology and SNAP Perinatal Extension)

SNAP II

Variables	Values	Points
Mean Blood Pressure	-	0
Lowest temperature	-	0
P02 (mmHg) / FIO2 (%)	-	0
Lowest serum pH	-	0
Multiple seizures	-	0
Urine output (mL/kg.h)	-	0
	SNAP II : 0	
Apgar score	-	0
Birth weight	~	0
Small for gestational age (help)	*	0

SNAPPE II : 0 In-hospital mortality : see below Data are collected within the first 12 hours after admission to the NICU

Clear

Ref: D K. Richardson et al. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. J Pediatr 2001; 138: 92-100

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Gestational age (wk)	3rd percentile birth weight	(g)
-	0	

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Calibration of mortality risk model, by birth weight category (Logistic regression equation is not available)

		Observ	ed deaths	Expect	ted deaths
SNAPPE-II	Total	No.	%	No.	%
	F	or all bi	irth weight	s	
0-9	16,274	48	0.3%	51	0.3%
10-19	3,923	61	1.6%	61	1.6%
20-29	1,952	74	3.8%	71	3.6%
30-39	1,262	93	7.4%	101	8.0%
40-49	790	124	15.7%	116	14.7%
50-59	476	105	22.1%	102	21.4%
60-69	310	101	32.6%	100	32.3%
70-79	142	55	38.7%	63	44.4%
> = 80	141	94	66.7%	90	63.8%

		Obsen	ved deaths	Expect	ted deaths			Obser	ved deaths	Expec	ted deaths
SNAPPE-II	Total	No.	%	No.	%	SNAPPE-II	Total	No.	%	No.	%
		For	<1500 g					For>	=1500 g		
0-9	1,526	9	0.6%	7	0.5%	0-9	14,748	39	0.3%	45	0.3%
10-19	1,092	30	2.7%	24	2.2%	10-19	2,831	31	1.1%	37	1.3%
20-29	772	40	5.2%	38	4.9%	20-29	1,180	34	2.9%	33	2.8%
30-39	645	61	9.5%	60	9.3%	30-39	617	32	5.2%	40	6.5%
40-49	497	79	15.9%	78	15.7%	40-49	293	45	15.4%	38	13.0%
50-59	318	72	22.6%	72	22.6%	50-59	158	33	20.9%	30	19.0%
60-69	260	85	32.7%	84	32.3%	60-69	50	16	32.0%	16	32.0%
70-79	121	46	38.0%	53	43.8%	70-79	21	9	42.9%	10	47.6%
> = 80	132	88	66.7%	85	64.4%	> = 80	9	6	66.7%	5	55.6%