Plasma Lactate Levels : A Tool for Prognosis in Cases of Plasmodium Falciparum Malaria

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ABSTRACT

Background :

Malaria still remains unconquered and is a heavy burden on tropical countries like India. Falciparum malaria is on the upsurge, a rampant infectious cause of multiorgan dysfunction. There is need to identify patients at risk of complications and adverse outcomes on admission for intensified care to reduce mortality.

Aim:

To study the plasma lactate in patients of malaria, correlate it with complications of Falciparum malaria and to evaluate its use as a prognostic marker.

Material and Methods :

In a prospective, analytical, observational study, 105 cases of HRP2 and/or PS positive cases of Falciparum malaria were evaluated. Plasma Lactate levels were estimated by Randox kit on admission in GMC, Nagpur. A total of 105 cases (mean age 36.43 $\pm$ 12.63 yrs, 61M /44F) were included in the study. They were divided into two groups – Survivors (n=70) and Non survivors (n=35).

Results :

Mean plasma lactate level in survivors was 2.43 $\pm$ 0.62 mmol/lt, while that in non survivors was 4.18 $\pm$ 0.58 mmol/lt ($p<0.001$ at 95% confidence interval). Mean plasma lactate values in survivors with complications was 2.62 $\pm$ 0.56 mmol/lt as compared to uncomplicated cases 1.99 $\pm$ 0.50 mmol/lt ($p<0.001$ at 95% confidence interval).

All cases in non survivors had complications. The mean plasma lactate in cases with 1, 2, 3, 4 and 5 complications was 2.53 $\pm$ 0.57, 2.52 $\pm$ 0.59, 2.54 $\pm$ 0.49, 3.08 $\pm$ 0.23 and 3.26 $\pm$ 0.12 in the survivor group and 3.52, 3.92 $\pm$ 0.41, 4.15 $\pm$ 0.46, 4.51 $\pm$ 0.92 and 4.46 $\pm$ 0.5 in the non survivor group respectively. ($p<0.05$ at 95 % confidence interval). The mortality rates in in the cases with 1, 2, 3, 4 and 5 complications were 8%, 57%, 75%, 60% and 60% respectively. More than 5 complications were seen in only 1 case (non survivor) with lactate level of 4.4 mmol/lt. Plasma lactate > 4 mmol/lt was found to be significantly ($p<0.001$) associated with mortality.

Conclusion :

Plasma lactate is a good indicator of prognosis and outcome in Falciparum malaria and it should be used for prognostication of patients with high risk of complications and adverse outcome for intensive care.

Introduction

Infectious diseases remain a major cause of death and debility worldwide, of which the top five are HIV/AIDs, Diarrhoea, Tuberculosis, the Childhood Clusters (Measles, Pertussis, Tetanus, Diphtheria and Poliomyelitis) and Malaria (The World Health Report 2004). Malaria is the most important eukaryotic parasitic disease, threatening the livelihood of over 2.2 billion people[1] and causes almost all of the 1.7-2.5 million deaths worldwide from Malaria.[2, 3, 4] Malaria

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remains today as it has been for centuries – a heavy burden on tropical countries like India, with drug resistance compounding the problem. Malaria, especially falciparum malaria, can cause various complications involving various systems of the body. Cerebral malaria, acute renal failure, black water fever, hypoglycaemia, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), hypotension and shock are among the common manifestations of complicated malaria. Complicated malaria in pregnant women and in patients with HIV co-infection has increased morbidity and mortality. Healthcare costs are soaring and P. Falciparum being the most virulent of the malarial species, with a multitude of complications associated with it, there is an acute need to identify patients at risk of developing complications and to intensify care given to these patients so that the burden of morbidity and high mortality is reduced. There are a number of predictors of prognosis in malaria that can be used to identify this risk group. This study was undertaken to evaluate plasma lactate level as a prognostic indicator of disease severity and outcome.

Methods

This prospective, analytical, observational study was conducted at a tertiary care hospital (Govt. Medical College and Hospital, Nagpur) over a period of 18 months (Jan 2007 to Sept 2008). 105 adult cases (n=105) of documented falciparum malaria i.e. either HRP2 positive and or Peripheral smear positive cases admitted in Intensive care unit and general wards of Medicine Dept. were included. These were excluded for other systemic illnesses. These were thoroughly interrogated with regards to presenting complaints like fever, chills/rigors, jaundice, urine output, swelling over the body, breathlessness, bleeding tendencies, altered sensorium, convulsions etc. Vital parameters, clinical signs at admission like pallor, icterus, oedema, bleeding manifestations were noted and thorough systemic examination was done. The Glasgow Coma Score was also calculated for each. Blood investigations like peripheral smears, complete blood counts, platelet count, urea and creatinine levels, total bilirubin, SGPT, SGOT, Blood glucose levels, electrolytes, arterial blood gases were obtained. Parasite index was calculated. Blood sample for plasma lactate level at admission was collected from a stasis free vein in a fluoride EDTA bulb. Plasma was separated by centrifugation within 30 minutes and processed by Randox kit for estimation of plasma lactate levels using Biochemistry Analyzer TRACE 30 v4.1. Patients were classified as Complicated malaria and Uncomplicated malaria as per the WHO Criteria for Severe Falciparum Malaria[5]. Data collected was systematically tabulated and analysis was done using standard statistical software SPSS version 15.0.

T-test was used for continuous normally distributed variables. For categorical data chi-square statistics was used and Fischer-exact test was used for small numbers. For the variables which were not normally distributed Wilcoxon's-Mann-Whitney test was used. $P< 0.05$ was considered as a statistical significance at 95% confidence intervals. Multi variate analysis was done using multilinear regression analysis for various complications of falciparum malaria and outcome, also using it for comparison with lactate levels.

Results

Majority of the patients were middle aged with 27 (25.71%) cases between 21 to 30 years, 23 (21.9%) cases in 31 – 40 year age, and 31 (29.52%) cases were between 41 to 50 years of age. The sex distribution of the cases showed that 61 patients (58.1%) were males as compared to 44 females (41.9%). The overall mean age of subjects in the study was 36.43±12.63 years .

Of the 105 study subjects, there were 70 (66.66%) survivors while 35 (33.34%) patients succumbed. Of the 70 survivors, 48 cases (68.57%) having some form of severe/complicated falciparum malaria, whereas all of the 35 cases (100%) who succumbed were having complications (table 1).

Raised plasma Lactate levels were significantly associated with mortality ($p<0.001$, at 95% confidence interval) (table 4).

A GCS < 11 and a respiratory rate > 20 was significantly associated with mortality ($p<0.001$, at 95% confidence interval). The presence of renal failure was significantly associated with mortality ($p=0.002$, at 95% confidence interval). The presence of pH<7.25, HCO3 <15 mmol

were significant in their association with mortality (p<0.001, at 95% confidence interval). The presence of coagulopathy was significantly associated with mortality . (table 2)

The mean plasma Lactate level in survivors was 2.43 ± 0.62 mmol/lt. While the same in the non survivor group was 4.18 ± 0.58 mmol/lt. The mean Lactate level in survivors without any complication (n=22) was 1.99 ± 0.53 mmol/lt, but that in survivors with complications (n=48) was 2.62 ± 0.56 mmol/lt. (table 4)

Analysis of plasma Lactate levels in the survivors showed that only 1 (1.43%) case had markedly raised lactate levels and had complications. Remarkably amongst the non survivors none of the case had plasma lactate level in the normal range. Mild to moderately raised lactate (2.2 – 4 mmol/lt) was seen in 18 (51.43%) cases. Markedly raised lactate (>4 mmol/lt) was seen in 17 (48.57%) cases. Hyperlactatemia (>5 mmol/lt) was seen in 3 (8.57%) cases of non survivors. A Plasma lactate level more than 4 was significantly associated with prognosis and mortality (p<0.001, at 95% confidence interval). One notable point was that even though texts mention hyperlactatemia > 5 mmol/lt as a marker of poor prognosis in Falciparum Malaria, in our study it was observed that only 3 cases had such high levels. In cases who had adverse outcomes a lactate level > 4 mmol/lt was also significantly associated with worse outcomes. The mean lactate levels in cases without complications (complication = 0) was 1.96 ± 0.46 mmol/lt (table 5).

It was seen that raised lactate levels in patients with complications were significantly related to a poor prognosis and to mortality. (table 6)

The mean lactate levels in survivors and non survivors with a single complication were 2.53 ± 0.57 and 3.52 ± 0.0 mmol/lt respectively. In cases with 2 complications, the mean lactate values in survivors and non survivors were 2.52 ± 0.596 and 3.92 ± 0.41 mmol/lt respectively, it being significantly higher in non survivors (p <0.001, at 95% confidence interval). In cases with 3 complications, the mean lactate level in survivors was 2.54 ± 0.496 mmol/lt while that in non survivors was 4.15 ± 0.46 mmol/lt, again being significantly higher in non survivors (p<0.001, at 95% confidence interval). In the cases having 4 complications, mean plasma lactate values in survivors and non survivors were 3.08 ± 0.234 and 4.51 ± 0.92 mmol/lt respectively, it being significantly higher in non survivors (p= 0.017, at 95% confidence interval). Such a significant trend (p=0.002, at 95% confidence interval) was maintained in cases with 5 complications, the mean lactate levels in survivors and non survivors being 3.26 ± 0.129 and 4.46 ± 0.507 mmol/lt respectively. Only 1 case had more than 5 complications, the patient had a plasma lactate level of 4.4 mmol/lt and succumbed. (table 7)

Multivariate analysis through multiple regression analysis was done taking outcome as a constant, parameters like GCS, Hb, Bilirubin, Creatinine etc and Lactate levels as variables. Of various variables only Plasma Lactate levels were found to be significant on multivariate analysis (p<0.001, at 95% confidence interval). The Hazard ratio of lactate was very high (15719.72) as compared to those of GCS (0.242), Hb (0.321), creatinine (2.804), 24 hr urine output (9.472), Bilirubin (0.058), pH (14.187), bicarbonate levels (0.007) and Systolic BP (12.747). But all these parameters except for lactate levels did not have a significant p value. Correlation coefficient (rho = -0.781) was indicative of a negative correlation of high lactate levels with a favourable outcome. Thus we could infer that the lower the lactate levels the favourable the outcome but adverse outcome is associated with higher values of lactate.

Discussion

Malaria has emerged as one of the major dreads of the century continuing in its mortality scale and a leading cause of morbidity in developing world. Falciparum malaria has raised its hood becoming fast a menacing killer in our subcontinent. Several factors play its aide including drug resistance, unique pathophysiology, potential for multiple organ system involvement, and climatic sustenance due to green house effect, all being catalysed by poverty, poor hygiene and illiteracy in a developing country like India. Thus the need of the hour, other than strong political motivation and health

policies by the governance, is the recognition of cases with potential for complication and multiorgan failure and intensified care to these patients in an effort to improve their outcome. Many predictors of outcome have been recognised by workers[5].

The processes of cytoadherence, rosetting and agglutination are central to the pathogenesis of falciparum malaria. They result in sequestration of red cells containing mature forms of parasite in vital organs particularly brain, heart, liver, spleen etc where they interfere with microcirculation and metabolism. Also, these sequestered parasites continue to develop out of reach of the principal host defence mechanisms: splenic processing and filtration.[5,6] In broad terms, the essential mechanism of death in falciparum malaria disease is agreed by many researchers: a functional tissue hypoxia that forces an unsustainable dependence on anaerobic metabolism. An unresolved key question is whether the tissue hypoxia arises (a) because insufficient oxygen reaches the mitochondria through either vascular occlusion from sequestered parasitized red cells acting alone, or in combination with anaemia or (b) because excessive release of inflammatory cytokines, induced by malarial toxin(s), renders mitochondria unable to use oxygen to generate energy from oxidative phosphorylation[7] Sequestered infected RBCs are metabolically active and release high amounts of lactic acid, leading to hypoglycaemia and lactic acidosis.[8,9] Anaerobic host tissue metabolism also produces large amounts of lactate in malaria patients.[10] Arterial, venous, capillary, and CSF concentration of lactate increases in proportion to the severity.

Lactic acidosis results from :

- Poor tissue perfusion, in some cases due to hypovolemia, leading to reduced oxygen delivery
- Lactate production by parasite
- Lactate generation as a result of cytokine activity especially TNF-α
- Reduced hepatic blood flow and hence lactate clearance
- Impaired renal function and thus acid clearance.[5,11]

We studied the usefulness of plasma Lactate levels as a predictor of mortality and outcome in our study due to its underplayed capacity as the same. The mean plasma Lactate level on admission in survivors was 2.43 ± 0.62 mmol/lt. While the same in the non survivor group was 4.18 ± 0.58 mmol/lt. Raised plasma Lactate levels were significantly associated with complications and mortality ($p<0.001$). One remarkable point was that even though literature mentions hyperlactatemia > 5 mmol/lt as a marker of poor prognosis in falciparum malaria, in our study it was observed that only 3 cases had such high levels. In cases who had adverse outcomes a lactate level > 4 mmol/lt was also significantly associated with worse outcomes. Hence studies to revise the threshold of hyperlactatemia, or levels significant in our subcontinent in contrast to western standards need to be undertaken.

SJ Allen, A O'Donnell, ND Alexander et al (1996) in their study of 489 children admitted with malaria found that a high level of plasma lactate was common (20%) and was the major predictor of death in multiple regression analysis.[12] Agbenyega T, Angus B et al (1997) studied blood lactate levels in 70 children with malaria (54 with severe malaria) and 48 control subjects. Plasma lactate levels were significantly elevated in patients with deep coma ($P = 0.0007$) and those with a fatal outcome.[13] M. Hatherill, A. G. McIntyre et al (2000) in their study group of 50 children with hyperlactataemia (lactate levels > 2 mmol/l enrolled), observed mortality was 32/50 (64 %). The median peak lactate level was 5 mmol/l (2–9.3) in survivors compared to 6.8 mmol/l (2.3–22) in nonsurvivors ($P = 0.02$), and the cumulative average lactate level was 2.4 mmol/l (1–4.9) in survivors, compared to 4.5 mmol/l (1.6–21) in nonsurvivors ($P = 0.0003$).[14] Arnaud Dzeing-Ella, Pascal C, Nze Obiang (2005) noted that of 583 children with severe malaria, hyperlactataemia was present in 73 (15.7%) with an overall case fatality rate of 8.9%. Of the 52 deaths in the course of the study 20 (50% of the 40 with measurements) had hyperlactataemia. They inferred that hyperlactataemia (OR = 6.98, 95% CI = 3.5–13.8, $p = 0.0001$), is an independent predictor of a fatal outcome.[15]

Thus in conclusion, there is a burning need of a tool for identification of cases with a higher risk of

complications and adverse outcome in order to triage these for intensive and aggressive care. Plasma lactate levels correlate well with various complications of falciparum malaria and can be used as a prognostic indicator. Plasma lactate levels also are significantly associated with mortality and can be reliably used as a predictor of outcome more often than seldom.

Table 1. Distribution of Study Subjects as per outcome and complications.

	Complicated	Uncomplicated	Total
Survivors	48	22	70 (66.66%)
Non survivors	35	0	35(33.34%)
Total	83(79.04%)	22(20.96%)	105

Table 2. Clinical Profile of Study Subjects

	Survivors (n=70)	Non survivors (n=35)	p value
Mean temperature (o F)	100.8 ± 1.04	101.25 ± 1.09	0.04
Mean Glasgow Coma Score	13.17 ± 2.86	9.68 ± 3.96	<0.001
GCS < 11	23(32.85%)	27(77.14%)	<0.001
Respiratory rate > 20 breaths/min	8(11.42%)	18(51.42%)	<0.001
Mean Parasite Index (%)	0.68 ± 1.07	1.73 ± 2.82	0.007
Mean Hb (gm%)	7.87 ± 1.84	7.15 ± 1.93	0.06
Platelets < 80000	13(18.57%)	13(37.14%)	0.01
Mean serum Creatinine (mg/dl)	2.56 ± 2.04	4.0 ± 2.80	0.003
S Creatinine > 3 (mg/dl)	20(28.57%)	21(60%)	0.002
Mean pH	7.34 ± 0.06	7.27 ± 0.08	<0.001
Mean Bicarbonates (mmol/lt)	21.82 ± 3.37	15.99 ± 5.18	<0.001
pH < 7.25	5 (7.14%)	12 (34.28%)	0.001
Mean rise in PT (s)	1.12 ± 1.96	4.74 ± 4.82	<0.001
Mean rise in PTTK (s)	0.87 ± 1.85	3.91 ± 4.37	<0.001
PT deranged > 3 s	8 (11.42%)	17(48.57%)	<0.001

Table 3. Mean Plasma Lactate Levels in Study Subjects

	Survivors (n=70)	Non survivors (n=35)	p value
Complicated	2.62 ± 0.56 (n=48)	4.18 ± 0.58 (n=35)	<0.001
Uncomplicated	1.99 ± 0.53 (n=22)	-	-
Total	2.43 ± 0.62	4.18 ± 0.58	<0.001

Table 4. Distribution of Plasma Lactate Levels in Study Subjects

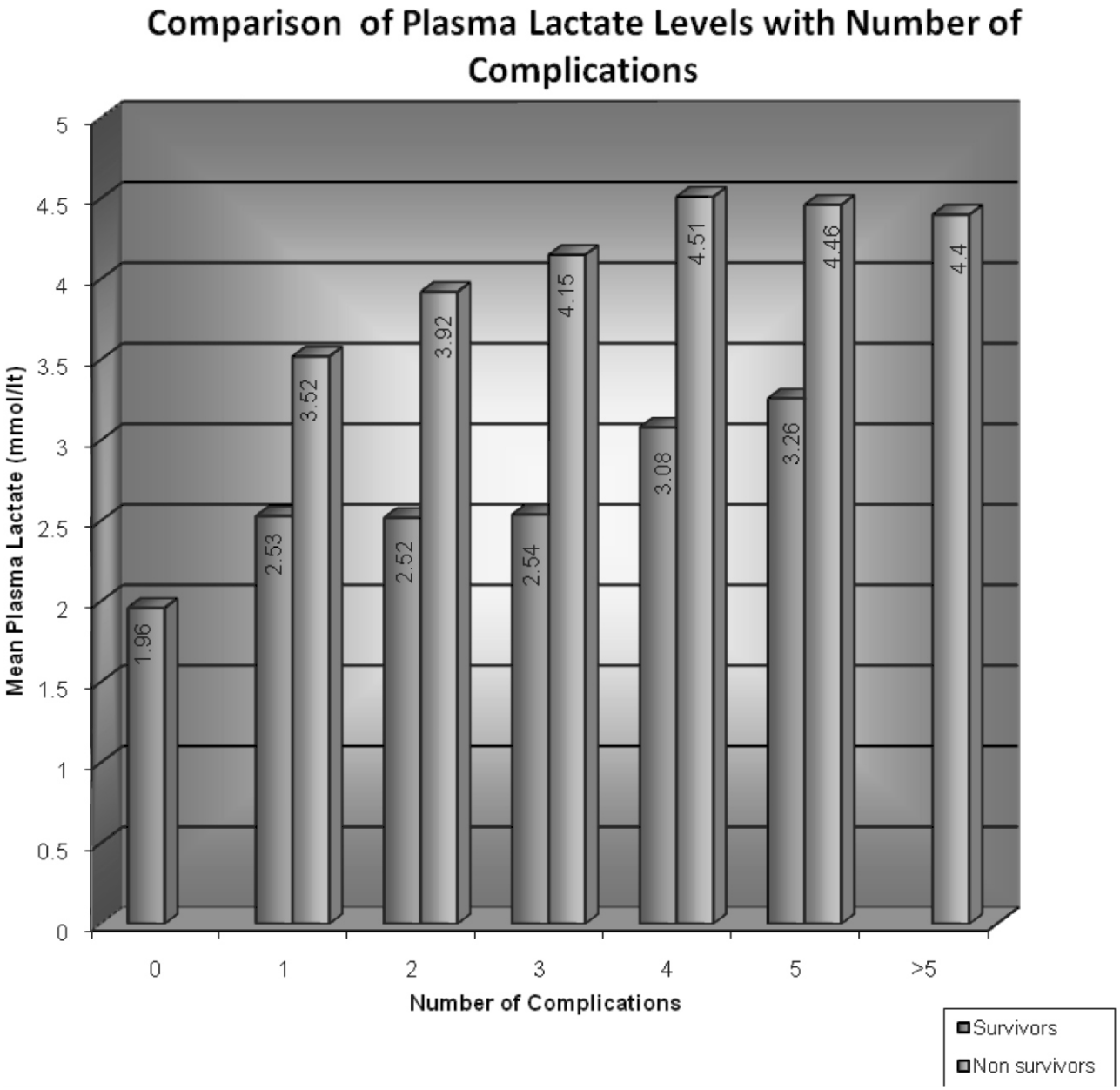
Pl. lactate level	Survivors (n=70)		Non survivors	p value
(mmol/lt)	Total (n=70)	Complicated (n=48)	(n=35)	
0.5 – 2.2	30 (42.85%)	13 (27.08%)	0	-
2.2 – 4	39 (55.72%)	34(70.83%)	18 (51.43%)	0.193
> 41	(1.43%)	1 (2.08%)	17 (48.57%)	<0.001
> 5	0	0	3 (8.57%)	-

Table 5. Comparison of Plasma Lactate Levels with Complications of Falciparum Malaria

Complication	Mean Pl. Lactate			p value
	Overall	Survivors	Non survivors	
GCS ≤ 11	3.6 ± 0.89 (n=50)	2.87 ± 0.57 (n=23)	4.22 ± 0.64 (n=27)	<0.001
Hb ≤ 5 gm%	3.26 ± 0.88 (n=16)	2.6 ± 0.52 (n=9)	4.11 ± 0.30 (n=7)	<0.001T
Bilirubin > 3 mg/dl	3.21 ± 0.82 (n=50)	2.67 ± 0.47 (n=30)	4.03 ± 0.48 (n=20)	<0.001
S Creatinine > 3 mg/dl	3.57 ± 1.08 (n=41)	2.68 ± 0.66 (n=20)	4.42 ± 0.6 (n=21)	<0.00124
hr urine output < 400 ml	3.84 ± 0.89 (n=21)	2.99 ± 0.35 (n=9)	4.47 ± 0.58 (n=12)	<0.001
SBP < 80 mm Hg	4.0 ± 0.8 (n=4)	2.8 (n=1)	4.4 ± 0.0 (n=3)	-
pH < 7.25	4.14 ± 0.84 (n=17)	3.15 ± 0.22 (n=5)	4.56 ± 0.62 (n=12)	<0.001
HCO3 < 15 mmol	4.07 ± 0.92 (n=14)	2.97 ± 0.20 (n=4)	4.51 ± 0.68 (n=10)	<0.001
ARDS	4.21 ± 0.87 (n=16)	3.10 ± 0.36 (n=6)	4.28 ± 0.52 (n=10)	<0.001
DIC	3.99 ± 0.91 (n=24)	3.05 ± 0.55 (n=8)	4.46 ± 0.66 (n=16)	<0.001

Table 6. Comparison of Plasma Lactate Levels with Number of Complications

		Mean Pl. Lactate (mmol/lt)		p value
No. of Complications	Total no. of cases	Survivors	Non survivors	
0	22	1.96 ± 0.46 (n=22)	0	-
1	25	2.53 ± 0.57 (n=23)	3.52 ± 0.0(n=2)	-
2	21	2.52 ± 0.596 (n=13)	3.92 ± 0.41 (n=12)	<0.001
3	16	2.54 ± 0.496 (n=4)	4.15 ± 0.46 (n=12)	<0.001
4	10	3.08 ± 0.234(n=4)	4.51 ± 0.92 (n=6)	0.017
5	10	3.26 ± 0.129 (n=4)	4.46 ± 0.507 (n=6)	0.002
>5	1	0	4.4 (n=1)	-



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