Brief report

Continuous reference intervals for plasma cystatin C and creatinine in Vietnamese children

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Abstract

Background

Serum (plasma) creatinine and cystatin C are widely used in pediatric clinical practice to assess glomerular filtration rate. Both markers have limitations due to the low index of individuality, which affects the clinical sensitivity of population-based reference intervals, especially when wide age ranges are considered. This study aimed to establish age-related reference intervals for plasma cystatin C and creatinine in Vietnamese children.

Methods

A total of 454 children, equally divided between boys and girls, aged from 1 day to 18 years, were recruited from the outpatient clinic of Vietnam National Children's Hospital. None of the participants had kidney or infectious diseases. Plasma samples were analyzed for cystatin C and creatinine using standard clinical chemistry methods. Using the the Lambda-Mu-Sigma method, we derived centile charts showing dynamic changes in these biomarkers.

Results

In this cohort, plasma creatinine levels were high at birth, declined to their lowest point between ages of 2 and 3 years, and then gradually increased until adulthood. Plasma cystatin C levels were also elevated at birth, decreased to a steady state around age of 2 year, and remained stable until age of 10 years. From ages 10 to 14 years, cystatin C levels slightly increased, followed by a decrease from ages 15 to 18 years.

Conclusions

Accurate assessment of glomerular filtration in children requires reliable laboratory tests and age-specific reference intervals. Providing serum (plasma) cystatin C and creatinine reference intervals with appropriate age partitions is crucial for improving the clinical sensitivity for detecting renal dysfunction, especially during the first few years of life.

Introduction

Evaluation of renal function (glomerular filtration) in children plays an important role in many clinical settings. Serum creatinine and creatinine clearance are widely used in pediatric clinical practice to assess glomerular filtration rate. However, serum creatinine concentrations are affected by muscle mass, age, and diet, which can confound its assessment of glomerular filtration in children [1, 2]. An alternate surrogate biomarker for glomerular filtration is cystatin C. Cystatin C is a low molecular weight serine protease inhibitor that is produced by all human nucleated cells at a steady rate. Cystatin C is freely filtered through the glomerular membrane and is mostly reabsorbed and catabolized by the proximal tubule cells of the kidney. Unlike creatinine, it is not affected by factors such as diet or muscle mass [3, 4]. An equation for estimated glomerular filtration rate in children has been described for cystatin C, which facilitates improved glomerular filtration assessment for this population [5].

A study comparing the biological variation of serum cystatin C and serum creatinine in children showed that the within-subject variations of these two markers are similar and suggested that they are both suitable for monitoring renal function in children [6]. However, the within-subject biological variation is small relative to the between-subject biological variation (i.e., low index of individuality) for both serum creatinine and cystatin C. When population-based reference intervals are applied to individual patients, they are much wider than the within-subject biological variation of the patient, and a relatively large pathology or abnormality may be required for the patient result to exceed the reference intervals [6]. In other words, the serum cystatin C or serum creatinine of an unwell child may have to deviate significantly from his physiologic set point before exceeding the population-based reference intervals. This limitation is particularly pronounced when a reference interval with a wide age interval is adopted since the reference limits may be widened to accommodate larger age-related changes.

To overcome this limitation, continuous age-related reference intervals that closely describe the underlying dynamic distribution may be adopted to improve their clinical sensitivity [7-9]. In this study, we measured plasma cystatin C and creatinine, and described the continuous, age-related reference intervals in a cohort of Vietnamese children.

Subjects and methods

A total of 454 children with equal numbers of boys and girls, aged from 1 day to 18 years, who attended the outpatient clinic of Vietnam National Children's Hospital between December 2020 and June 2021, and did not present with kidney disease or infectious disease, were recruited in this study. The exclusion criteria were as follows: 1) patients with nephropathy, digestive system diseases, acute or chronic infections, metabolic or nutritional diseases, autoimmune diseases, thyroid diseases, blood disorders, heart diseases, malignant tumors, burns, muscle damage, obesity or weight loss, or hypertension; 2) patients with blood transfusion; 3) preterm neonates. The children's parents provided informed consents following explanation of the study protocol, which had been approved by the local ethics committee (2374/BVNTW-HĐĐĐ) and complied with the Helsinki Declaration. Venous blood samples were collected into heparin tubes. Samples were centrifuged at 5000 rpm for 5 min, plasma was separated into 1.5 ml tube (Eppendorf). Residual plasma (stored at -80oC) from these children was subjected to cystatin C and creatinine measurements following routine clinical chemistry testing at the biochemistry laboratory at National Children's Hospital, which is accredited to ISO 15189 by the Bureau of Accreditation in Vietnam.

Plasma cystatin C was measured using the Tina-quant Cystatin C Gen.2 on the Cobas c501 platform (Roche Diagnostics, Hanoi, Vietnam), according to manufacturer instructions. This measurement procedure was traceable to the National Institute of Standards and Technology Standard Reference Material 909b Level 2. The analytical measurement range of this measurement procedure was 0.40–6.80 mg/L. The coefficient of variations for within-run and between-run imprecision were <2.2% based on three quality control samples with cystatin C concentrations between 1.11 and 4.14 mg/L. Plasma creatinine was analyzed using a kinetic uncompensated Jaffe method on the AU5800 platform (Beckman Coulter Inc., Hanoi, Vietnam). This creatinine measurement procedure was traceable to the Isotope Dilution Mass Spectroscopy method via National Institute of Standards and Technology Standard Reference Material 967. The analytical measurement range of the serum creatinine measurement procedure was 18- 2200 µmol/L. The coefficient of variation for within-run and between-run imprecisions of this measurement procedure derived from quality control samples was <2%.

The plasma cystatin C and creatinine measurements against age were visualized on scatter plots, which did not reveal any gross outlier. There was no statistically significant difference (two tailed student t-test, $p>0.05$) between boys and girls for both measurands and the datasets of both genders were combined. Subsequently, the cystatin C and creatinine datasets were subjected to the Lambda-Mu-Sigma (LMS) method to derive centile charts using the LMS Chartmaker Pro software [10]. For plasma creatinine, subjects below 30 day-olds (n = 21) were excluded from analysis as a good fit could not be achieved in the software due to high variance and relatively low data density. The default Lambda, Mu, Sigma (i.e. L, M, S) parameters were set at 3.0, 5.0, and 3.0 equivalent degrees of freedom, respectively, and represented optimal fitting parameters with lowest deviations following adjustments. Smoothed curves were generated for the 2.5^{th}, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}, and 97.5^{th} centiles, respectively.

Results and Discussion

The scatter plots and continuous centile (reference intervals) charts for plasma creatinine and cystatin C of the children are shown in Figure 1. Plasma cystatin C concentrations were high

at birth and declined, reaching a steady state around 2 years of age (Figure 2). The median cystatin C concentrations remained stable throughout up to the age of 10 years, and slightly increased from 10 -14 years of age, then decreased in children aged 15-18 years. On the other hand, plasma creatinine concentrations were elevated after birth and dropped quickly after the newborn period. It subsequently rose continuously until 18 years old (Figure 3). The numerical centile values for plasma cystatin C and creatinine at discrete ages are provided as a Supplemental Tables.

Figure 1: Scatter plot of plasma cystatin C (right y-axis) and creatinine (left y-axis) in Vietnamese children aged 0-18 years.

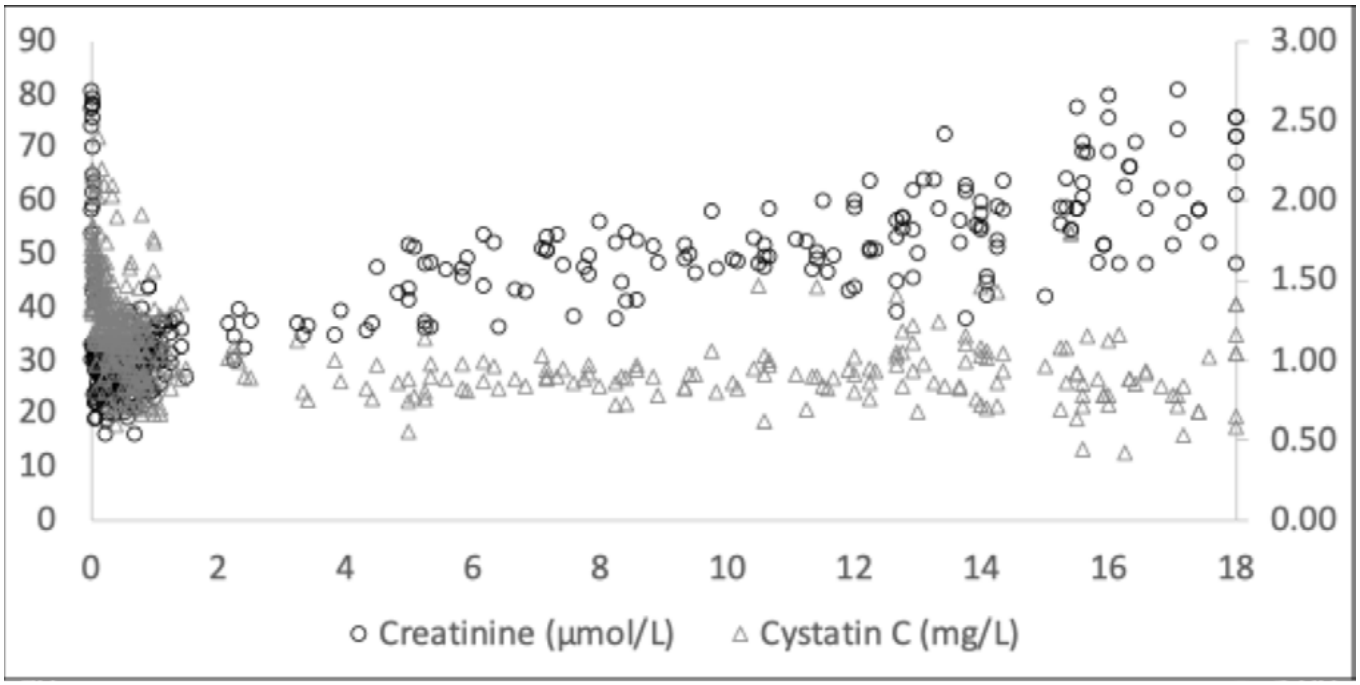


Figure 2: Continuous centile charts presenting 2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5th centiles of plasma cystatin C in Vietnamese children aged 0-18 years.

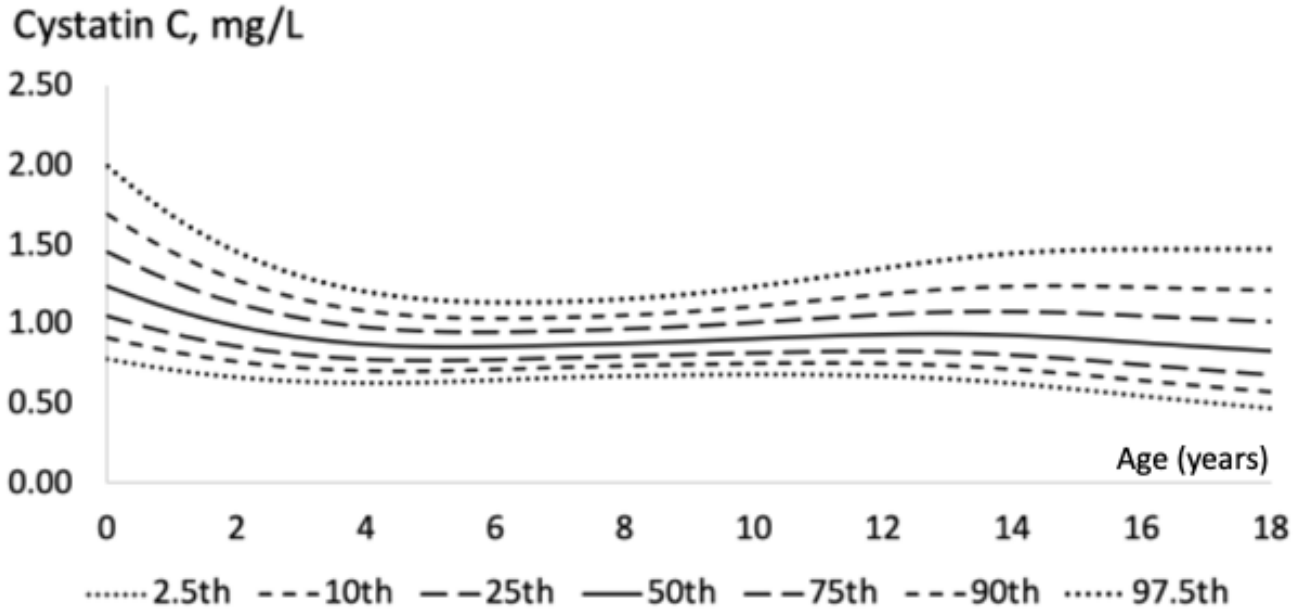
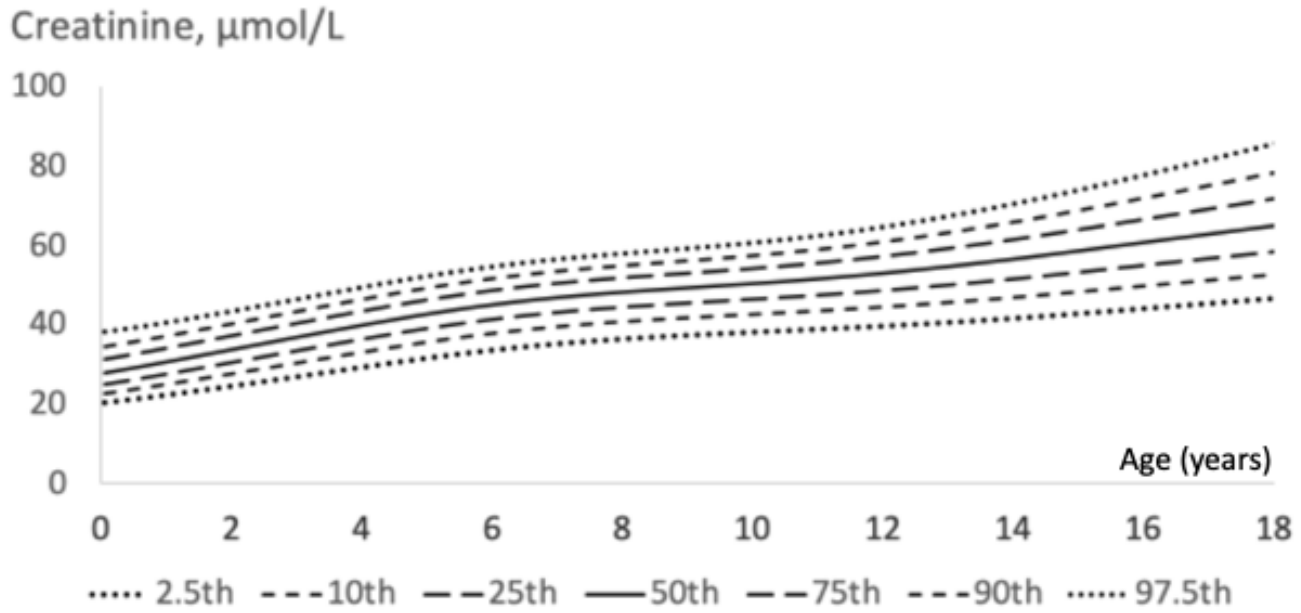


Figure 3: Continuous centile charts presenting 2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5th centiles of plasma creatinine in Vietnamese children aged 0-18 years.



This study provides the reference values for plasma cystatin C and creatinine in a cohort of Vietnamese children without known renal conditions and fills an important knowledge gap for this ethnicity. The plasma cystatin C in this cohort of Vietnamese children was elevated at birth and declined continuously until it stabilizes at 2 years of age, when it remained relatively stable (albeit with a mild increase) until after age 14 when it starts to mildly decline. These findings were largely in line with previous literature although some differences are noted. In this study, we did not find a statistical difference in plasma cystatin C distribution between genders. In contrast, Ziegelasch et al. found gender differences in cystatin C, especially during infancy and puberty in a cohort of 2803 healthy German children. They also reported a mild increase of median cystatin C for both boys and girls at ages 11 to 14 years [11].

At the same time, Liu et al. reported significantly higher serum cystatin C levels in boys aged 4-18 years old compared to girls in a cohort of 4765 healthy Chinese children [12]. Conversely, Cai at al. observed a slight increase in serum cystatin C for males whilst continuous decrease for females after the age of six years in a different cohort of healthy Chinese children [13]. More recently, van Donge et al. found that gender-dependent changes in cystatin C that decreased at birth with age until approximately 2 years, thereafter, increased with age [14]. The differences in the observed dynamic changes in cystatin C in the published studies surveyed above may be related to differences in ethnicity, study population, study design, statistical technique, and sample size.

The plasma creatinine in our Vietnamese cohort was elevated at birth and decline to reach a nadir between ages 2 and 3 years before gradually rising until adulthood. This dynamic change is broadly similar to reports in other populations including Australia, Canada and Germany [7, 9, 15]. Like serum cystatin C, the dynamic change in plasma creatinine concentration throughout childhood suggested a need for age-specific reference intervals for optimal result interpretation in children. Ideally, the age-specific reference intervals should be provided in a continuous manner instead of partitioned by wide age intervals. This consideration is underscored by a study comparing continuous reference intervals for serum creatinine to reference intervals with discrete age partition from the CALIPER study [9]. This study noted a deficiency in representing the age dependence of creatinine concentration with distinct age intervals, which is especially apparent when a child advances across age intervals, e.g., from neonate (0–14 days; 28.3 – 81.4 µmol/L) to infancy (15 days to 2 years; 8.8 – 31.8 µmol/L), where a 3-fold difference in the reference limits may be observed [9].

The key limitations of this study are the relatively small number of children recruited, which may obscure gender-related trends as well as the lack of formal assessment for underlying renal conditions and active infections in the children recruited. These limitations were related to the resource availability of the study team and were mitigated by representative sampling of subjects across the ages with over-representation in the first few years of life where changes are more dynamic and careful case selection from the outpatient clinic.

Conclusion

Proper assessment of glomerular filtration (‘renal function’) in children is dependent on both the availability of reliable laboratory tests and reference intervals to guide result interpretation. While it is ideal to report continuous reference intervals for measurands that change dynamically with age, it remains a challenge with

most of the laboratory informatics system in use currently. Nonetheless, it is important that serum (plasma) cystatin C and creatinine reference intervals are provided with appropriate age partition to account for the dynamic changes, particularly in the first few years of life to improve the clinical sensitivity for renal dysfunction.

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Author Contributions
All authors contributed to the development and analysis of this study. Dr. Mai developed the project plan. Dr Ha and Ms. Dung selected participants and perform sample analysis in the Clinical Biochemistry Laboratory, National Children's Hospital, Vietnam. Dr Tze Ping Loh performed the statistical analysis. Dr Mai wrote the first draft of this manuscript and all authors reviewed, edited, and approved the final manuscript.

Conflicts of Interest
None to declare.

Research Funding
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Supplemental Data Table 1: Numerical centile values for plasma cystatin C at discrete ages.

Age (year)	Plasma cystatin C concentration (mg/mL)						
	2.5th	10th	25th	50th	75th	90th	97.5th
0	0.7755909	0.9101604	1.051529	1.236179	1.45538	1.687861	1.994763
0.1	0.768464	0.9010174	1.039981	1.221079	1.435502	1.662303	1.960829
0.2	0.7613209	0.8918592	1.028429	1.206006	1.415716	1.636943	1.927287
0.3	0.754196	0.8827255	1.016919	1.191013	1.396086	1.611853	1.894226
0.4	0.7471327	0.8736659	1.005506	1.176168	1.37669	1.587125	1.86175
0.5	0.740173	0.8647284	0.994246	1.161534	1.357602	1.562842	1.829957
0.6	0.7333557	0.8559581	0.9831902	1.14717	1.338892	1.539084	1.798933
0.7	0.7267152	0.8473944	0.9723833	1.133129	1.320617	1.515914	1.768749
0.8	0.7202781	0.8390678	0.9618594	1.119447	1.30282	1.493378	1.739451
0.9	0.7140631	0.8309996	0.9516426	1.106153	1.285531	1.471505	1.711066
1	0.7080805	0.8232016	0.9417458	1.093261	1.268763	1.450307	1.6836
1.1	0.7023333	0.815677	0.9321723	1.080772	1.252517	1.429782	1.657046
1.2	0.696822	0.8084267	0.9229231	1.068688	1.236792	1.409927	1.631391
1.3	0.6915442	0.8014488	0.9139962	1.057005	1.221583	1.390731	1.60662
1.4	0.6864967	0.7947399	0.905388	1.045719	1.206883	1.372185	1.582713
1.5	0.6816757	0.7882959	0.8970938	1.034825	1.192684	1.354275	1.559649
1.6	0.6770771	0.7821128	0.889109	1.024316	1.178977	1.336988	1.537409
1.7	0.6726971	0.7761862	0.8814287	1.014185	1.165753	1.320313	1.515973
1.8	0.6685318	0.7705119	0.8740479	1.004427	1.153002	1.304235	1.49532
1.9	0.6645771	0.7650855	0.8669616	0.9950349	1.140718	1.288743	1.475432
2	0.6608291	0.7599028	0.860165	0.9860027	1.128889	1.273823	1.45629
2.1	0.6572839	0.7549596	0.853653	0.9773238	1.117508	1.259464	1.437875
2.2	0.6539376	0.7502513	0.8474206	0.968992	1.106566	1.245654	1.42017
2.3	0.6507862	0.7457737	0.841463	0.9610009	1.096054	1.23238	1.403156
2.4	0.6478267	0.7415237	0.8357761	0.9533455	1.085966	1.219632	1.386818
2.5	0.6450567	0.7374985	0.8303569	0.9460214	1.076294	1.207402	1.371142
2.6	0.6424736	0.7336952	0.8252019	0.939024	1.067032	1.195678	1.356112
2.7	0.6400748	0.7301108	0.8203074	0.9323483	1.058172	1.184451	1.341715
2.8	0.6378572	0.7267419	0.8156694	0.925989	1.049708	1.173711	1.327934
2.9	0.6358179	0.7235852	0.8112838	0.9199407	1.041633	1.163448	1.314755
3	0.633954	0.7206373	0.8071466	0.9141983	1.033938	1.153651	1.302165
3.1	0.6322625	0.7178949	0.8032538	0.9087565	1.026616	1.144311	1.290148
3.2	0.6307403	0.7153545	0.7996013	0.90361	1.019661	1.135419	1.278693
3.3	0.6293845	0.7130128	0.796185	0.8987536	1.013066	1.126965	1.267785
3.4	0.6281929	0.710867	0.793002	0.8941833	1.006824	1.118941	1.257414
3.5	0.6271634	0.7089151	0.7900493	0.8898953	1.000931	1.111341	1.247568
3.6	0.6262926	0.707153	0.7873226	0.8858841	0.9953799	1.104154	1.238237
3.7	0.6255767	0.7055766	0.7848167	0.8821434	0.990162	1.097371	1.229406
3.8	0.625012	0.7041815	0.7825266	0.8786672	0.9852698	1.090982	1.221063
3.9	0.6245944	0.7029632	0.7804474	0.8754492	0.9806958	1.084978	1.213194
4	0.6243209	0.7019182	0.7785747	0.8724844	0.9764335	1.07935	1.205791
4.1	0.6241887	0.7010434	0.7769051	0.8697683	0.9724771	1.07409	1.198842
4.2	0.6241949	0.7003356	0.7754349	0.8672964	0.9688208	1.069193	1.192338

4.3	0.6243367	0.6997916	0.7741601	0.8650641	0.9654588	1.06465	1.186269
4.4	0.624611	0.6994081	0.7730773	0.8630669	0.9623855	1.060454	1.180627
4.5	0.6250146	0.6991812	0.7721819	0.8612995	0.9595945	1.056598	1.175402
4.6	0.6255431	0.6991062	0.7714685	0.8597555	0.9570782	1.053072	1.170581
4.7	0.6261925	0.6991785	0.7709321	0.858429	0.9548293	1.049868	1.166156
4.8	0.6269592	0.6993942	0.7705681	0.8573147	0.9528415	1.046978	1.162116
4.9	0.6278396	0.6997492	0.7703718	0.8564072	0.9511083	1.044395	1.158452
5	0.6288297	0.7002391	0.7703385	0.8557008	0.9496233	1.042111	1.155155
5.1	0.6299246	0.7008584	0.7704622	0.8551887	0.9483784	1.040117	1.152214
5.2	0.6311138	0.701596	0.7707305	0.8548575	0.9473585	1.038395	1.149609
5.3	0.6323847	0.7024382	0.771129	0.8546911	0.946546	1.036926	1.147319
5.4	0.6337251	0.703372	0.7716436	0.8546742	0.9459238	1.035692	1.145322
5.5	0.6351253	0.7043869	0.7722631	0.8547947	0.9454787	1.034678	1.143602
5.6	0.6365758	0.7054731	0.7729771	0.8550413	0.9451985	1.033871	1.142145
5.7	0.6380678	0.7066212	0.7737756	0.8554033	0.9450715	1.033258	1.140936
5.8	0.6395922	0.7078215	0.7746487	0.8558699	0.9450859	1.032826	1.139961
5.9	0.6411402	0.709065	0.7755865	0.8564308	0.9452308	1.032564	1.139208
6	0.6427038	0.7103431	0.7765801	0.8570764	0.9454957	1.032459	1.138665
6.1	0.6442747	0.7116472	0.7776204	0.857797	0.9458702	1.032502	1.138318
6.2	0.6458446	0.7129685	0.7786981	0.8585827	0.9463438	1.032681	1.138156
6.3	0.647406	0.7142989	0.7798051	0.8594247	0.946907	1.032986	1.138168
6.4	0.6489526	0.7156324	0.7809346	0.8603161	0.9475526	1.033408	1.138347
6.5	0.6504794	0.7169635	0.7820812	0.8612512	0.9482746	1.033943	1.138685
6.6	0.6519814	0.7182871	0.7832397	0.8622246	0.9490674	1.034583	1.139175
6.7	0.6534535	0.7195979	0.7844045	0.8632306	0.9499248	1.035323	1.139813
6.8	0.6548906	0.7208908	0.7855704	0.8642635	0.9508411	1.036157	1.140591
6.9	0.6562881	0.7221609	0.7867322	0.865318	0.9518107	1.037078	1.141503
7	0.657641	0.723403	0.7878846	0.8663885	0.9528278	1.038082	1.142543
7.1	0.6589442	0.7246118	0.7890218	0.867469	0.9538858	1.03916	1.143705
7.2	0.6601934	0.7257826	0.7901393	0.8685545	0.9549797	1.040308	1.144982
7.3	0.6613867	0.7269136	0.7912351	0.8696433	0.956108	1.041524	1.146374
7.4	0.6625239	0.7280048	0.7923091	0.8707354	0.9572707	1.04281	1.147881
7.5	0.6636052	0.7290565	0.7933621	0.8718317	0.958469	1.044165	1.149505
7.6	0.6646323	0.7300705	0.7943958	0.8729343	0.9597053	1.045593	1.151251
7.7	0.6656067	0.7310488	0.7954127	0.8740457	0.9609826	1.047098	1.153121
7.8	0.6665306	0.7319934	0.7964147	0.8751685	0.9623037	1.048682	1.15512
7.9	0.6674058	0.7329065	0.7974043	0.8763051	0.9636713	1.050349	1.157251
8	0.6682361	0.733792	0.7983858	0.8774601	0.9650904	1.052105	1.159522
8.1	0.6690257	0.7346546	0.799364	0.8786388	0.966567	1.053955	1.161938
8.2	0.6697787	0.7354985	0.8003434	0.8798462	0.9681063	1.055906	1.164507
8.3	0.6704991	0.7363281	0.8013285	0.8810869	0.9697135	1.057962	1.167235
8.4	0.6711892	0.7371455	0.8023218	0.8823635	0.9713913	1.060128	1.170126
8.5	0.6718495	0.7379513	0.8033236	0.8836763	0.97314	1.062404	1.17318
8.6	0.6724792	0.7387443	0.8043323	0.8850234	0.9749573	1.064787	1.176395
8.7	0.673077	0.7395229	0.8053461	0.8864027	0.9768411	1.067275	1.179769

8.8	0.6736437	0.7402876	0.8063654	0.8878142	0.9787909	1.069867	1.183301
8.9	0.6741797	0.7410387	0.8073903	0.8892579	0.9808069	1.072563	1.186991
9	0.6746858	0.7417769	0.8084211	0.8907341	0.9828888	1.075364	1.19084
9.1	0.6751616	0.7425014	0.8094569	0.8922412	0.9850351	1.078266	1.194844
9.2	0.6756063	0.743211	0.8104961	0.8937775	0.9872433	1.081269	1.199002
9.3	0.6760188	0.7439044	0.8115371	0.8953407	0.989511	1.084368	1.20331
9.4	0.6763983	0.7445803	0.8125781	0.8969287	0.9918354	1.08756	1.207765
9.5	0.6767427	0.745236	0.813616	0.8985379	0.9942124	1.090842	1.212361
9.6	0.6770495	0.7458684	0.814647	0.9001635	0.9966363	1.094206	1.217092
9.7	0.6773161	0.7464747	0.8156676	0.9018013	0.9991021	1.097646	1.22195
9.8	0.6775405	0.7470518	0.8166744	0.9034472	1.001605	1.101158	1.226928
9.9	0.6777214	0.7475982	0.817665	0.9050979	1.00414	1.104735	1.232021
10	0.6778576	0.7481119	0.8186371	0.9067506	1.006705	1.108373	1.237224
10.1	0.6779471	0.7485906	0.8195878	0.9084017	1.009294	1.112068	1.242529
10.2	0.6779881	0.7490321	0.8205141	0.9100472	1.011903	1.115813	1.24793
10.3	0.6779781	0.7494329	0.8214121	0.9116824	1.014526	1.119601	1.253419
10.4	0.6779135	0.7497889	0.8222767	0.913301	1.017156	1.123423	1.258983
10.5	0.6777913	0.7500961	0.8231031	0.9148972	1.019784	1.12727	1.264613
10.6	0.6776089	0.7503516	0.8238876	0.9164664	1.022406	1.131135	1.2703
10.7	0.6773661	0.7505546	0.8246292	0.918007	1.025019	1.135017	1.27604
10.8	0.6770613	0.7507032	0.8253256	0.9195161	1.027619	1.138909	1.281829
10.9	0.6766933	0.7507958	0.825975	0.9209917	1.030205	1.14281	1.287662
11	0.6762609	0.7508315	0.826576	0.9224318	1.032773	1.146716	1.293534
11.1	0.6757634	0.7508088	0.8271269	0.9238344	1.035322	1.150624	1.299442
11.2	0.6751996	0.7507265	0.8276263	0.9251977	1.037848	1.154529	1.305381
11.3	0.6745684	0.7505832	0.8280725	0.9265193	1.040348	1.15843	1.311345
11.4	0.673867	0.750376	0.8284619	0.9277952	1.042818	1.162318	1.317327
11.5	0.6730915	0.7501001	0.8287895	0.9290193	1.04525	1.166186	1.323315
11.6	0.6722397	0.7497531	0.8290524	0.9301884	1.04764	1.170029	1.329304
11.7	0.6713094	0.7493326	0.8292477	0.9312987	1.049984	1.173841	1.335286
11.8	0.6702977	0.7488351	0.8293713	0.9323458	1.052276	1.177616	1.341254
11.9	0.6692013	0.7482567	0.8294189	0.9333243	1.054511	1.181346	1.347198
12	0.6680173	0.7475938	0.8293862	0.934229	1.056681	1.185024	1.353109
12.1	0.6667425	0.7468427	0.8292688	0.9350548	1.05878	1.188642	1.358976
12.2	0.6653736	0.7459995	0.8290619	0.9357957	1.060802	1.192191	1.364789
12.3	0.6639075	0.74506	0.8287608	0.936446	1.062738	1.195662	1.370535
12.4	0.6623397	0.7440192	0.8283592	0.9369979	1.06458	1.199043	1.376202
12.5	0.6606652	0.7428709	0.82785	0.9374428	1.066316	1.202322	1.38177
12.6	0.6588791	0.741609	0.8272259	0.9377716	1.067936	1.205485	1.387224
12.7	0.6569764	0.7402276	0.8264796	0.9379756	1.069429	1.208519	1.392546
12.8	0.6549541	0.7387225	0.825606	0.9380481	1.070785	1.211412	1.397722
12.9	0.6528122	0.7370933	0.8246041	0.9379872	1.072003	1.214159	1.402745
13	0.6505522	0.7353413	0.8234746	0.9377928	1.07308	1.216759	1.407608
13.1	0.6481769	0.7334688	0.8222197	0.9374667	1.074017	1.219211	1.412311
13.2	0.6456884	0.7314779	0.820841	0.9370099	1.074816	1.221513	1.416848
13.3	0.6430883	0.7293699	0.8193396	0.9364229	1.075474	1.223664	1.421217

13.4	0.6403785	0.7271463	0.8177167	0.9357063	1.075992	1.225662	1.425411
13.5	0.6375613	0.7248095	0.8159742	0.9348612	1.076371	1.227505	1.429428
13.6	0.6346392	0.7223617	0.8141142	0.9338896	1.07661	1.229194	1.433264
13.7	0.6316147	0.7198051	0.8121386	0.9327925	1.07671	1.230726	1.436917
13.8	0.6284897	0.7171416	0.8100489	0.931571	1.076671	1.232101	1.440381
13.9	0.6252669	0.7143736	0.8078473	0.9302265	1.076494	1.233317	1.443653
14	0.6219498	0.7115045	0.8055369	0.9287619	1.07618	1.234375	1.446731
14.1	0.6185417	0.7085376	0.8031207	0.9271798	1.075732	1.235277	1.449614
14.2	0.6150467	0.7054771	0.8006033	0.9254843	1.075153	1.236023	1.452301
14.3	0.6114693	0.7023273	0.7979887	0.9236795	1.074446	1.236618	1.454795
14.4	0.6078137	0.6990929	0.7952816	0.92177	1.073616	1.237064	1.457098
14.5	0.604085	0.6957789	0.7924872	0.9197608	1.072668	1.237366	1.459213
14.6	0.6002884	0.6923907	0.789611	0.9176577	1.071607	1.23753	1.461144
14.7	0.5964291	0.6889338	0.7866586	0.9154664	1.070439	1.237561	1.462896
14.8	0.5925122	0.6854134	0.7836356	0.9131924	1.06917	1.237464	1.464474
14.9	0.5885428	0.6818349	0.7805473	0.9108413	1.067805	1.237245	1.465882
15	0.5845259	0.6782035	0.7773993	0.908419	1.06635	1.236909	1.467127
15.1	0.5804664	0.6745245	0.774197	0.9059309	1.064811	1.236462	1.468214
15.2	0.5763696	0.6708032	0.7709463	0.9033833	1.063194	1.235911	1.469149
15.3	0.5722407	0.6670454	0.7676527	0.900782	1.061505	1.235262	1.469938
15.4	0.5680845	0.6632561	0.764322	0.8981331	1.05975	1.23452	1.470588
15.5	0.5639067	0.6594414	0.7609604	0.8954433	1.057938	1.233695	1.471107
15.6	0.5597169	0.6556112	0.7575786	0.8927244	1.056081	1.232803	1.471518
15.7	0.5555238	0.6517746	0.7541862	0.8899872	1.054192	1.23186	1.471843
15.8	0.5513322	0.6479365	0.7507882	0.8872374	1.052279	1.230875	1.472094
15.9	0.5471467	0.6441016	0.7473899	0.8844813	1.05035	1.229858	1.472284
16	0.5429721	0.6402749	0.7439967	0.8817247	1.04841	1.228817	1.472425
16.1	0.5388123	0.6364605	0.7406129	0.8789725	1.046467	1.227761	1.47253
16.2	0.5346712	0.6326622	0.7372422	0.8762292	1.044526	1.226696	1.47261
16.3	0.5305529	0.6288839	0.7338889	0.8734993	1.042593	1.225632	1.472674
16.4	0.5264598	0.6251281	0.7305558	0.8707862	1.040671	1.224572	1.472732
16.5	0.5223921	0.6213956	0.7272437	0.8680911	1.038763	1.223519	1.472785
16.6	0.5183499	0.6176867	0.7239533	0.8654151	1.03687	1.222475	1.472835
16.7	0.5143335	0.6140019	0.7206857	0.8627595	1.034993	1.221441	1.472885
16.8	0.5103435	0.6103424	0.7174422	0.8601261	1.033134	1.22042	1.472936
16.9	0.5063805	0.6067091	0.7142242	0.8575169	1.031297	1.219415	1.472991
17	0.502445	0.603103	0.7110331	0.8549337	1.029483	1.218428	1.473053
17.1	0.4985373	0.5995249	0.7078702	0.8523781	1.027695	1.21746	1.473125
17.2	0.4946578	0.5959753	0.7047362	0.8498511	1.025933	1.216514	1.473205
17.3	0.4908053	0.5924533	0.7016302	0.8473518	1.024196	1.215588	1.473294
17.4	0.486978	0.5889568	0.69855	0.8448777	1.022481	1.214678	1.473385
17.5	0.4831737	0.5854836	0.6954931	0.8424258	1.020785	1.213779	1.473473
17.6	0.4793895	0.5820303	0.6924558	0.8399917	1.019102	1.212885	1.473549
17.7	0.4756228	0.5785937	0.6894341	0.8375708	1.017427	1.211989	1.473606
17.8	0.4718708	0.5751708	0.6864247	0.835159	1.015754	1.211085	1.473633
17.9	0.4681311	0.571759	0.6834245	0.8327524	1.014078	1.210167	1.473625

18	0.4644014	0.5683552	0.68043	0.8303469	1.012396	1.209228	1.473572
18.1	0.4606797	0.5649574	0.6774389	0.8279397	1.010702	1.208263	1.473469
18.167	0.4581907	0.5626845	0.6754369	0.8263261	1.009561	1.207603	1.473371

Supplemental Data Table 2: Numerical centile values for plasma creatinine at discrete ages.

Age (year)	Plasma creatinine concentration (µmol/L)						
	2.5th	10th	25th	50th	75th	90th	97.5th
0.05	20.39485	22.73694	25.0653	27.93971	31.15173	34.36477	38.35862
0.1	20.4914	22.85315	25.19565	28.08009	31.29369	34.49834	38.46825
0.2	20.6849	23.08624	25.457	28.3613	31.57795	34.76615	38.68958
0.3	20.87967	23.32091	25.71992	28.64389	31.86358	35.03593	38.91504
0.4	21.0766	23.55806	25.98532	28.92888	32.15176	35.30907	39.14625
0.5	21.27639	23.79837	26.25391	29.21702	32.44336	35.58656	39.38427
0.6	21.47948	24.04226	26.52609	29.50876	32.7389	35.86898	39.62972
0.7	21.68613	24.2899	26.80201	29.80424	33.03854	36.15651	39.88273
0.8	21.89625	24.54114	27.08148	30.10323	33.34201	36.44883	40.14284
0.9	22.10941	24.79547	27.36389	30.40506	33.64859	36.74512	40.409
1	22.32508	25.05229	27.64861	30.70904	33.95747	37.04445	40.68007
1.1	22.54292	25.31118	27.93517	31.01463	34.26808	37.34616	40.95522
1.2	22.76263	25.57179	28.22316	31.3214	34.57995	37.64973	41.2338
1.3	22.984	25.83384	28.51226	31.62901	34.89269	37.95473	41.51524
1.4	23.20685	26.09712	28.80227	31.93721	35.20607	38.26085	41.79917
1.5	23.43114	26.36157	29.09307	32.24592	35.51996	38.56798	42.08537
1.6	23.65686	26.62713	29.38463	32.55509	35.83434	38.87606	42.37371
1.7	23.88396	26.89375	29.67689	32.86465	36.14913	39.18499	42.66405
1.8	24.1124	27.16135	29.96975	33.17454	36.46426	39.49468	42.95622
1.9	24.3421	27.42984	30.26312	33.48464	36.77962	39.80502	43.25005
2	24.57303	27.69915	30.55692	33.79489	37.09514	40.11589	43.54537
2.1	24.80511	27.9692	30.85108	34.10519	37.41073	40.4272	43.84206
2.2	25.03828	28.23989	31.14548	34.41547	37.7263	40.73885	44.13995
2.3	25.27247	28.51115	31.44005	34.72564	38.04178	41.05075	44.43891
2.4	25.50762	28.7829	31.73471	35.03562	38.35709	41.36281	44.73882
2.5	25.74366	29.05505	32.02938	35.34534	38.67214	41.67492	45.03953
2.6	25.98052	29.32752	32.32397	35.65471	38.98687	41.98701	45.34093
2.7	26.21815	29.60023	32.6184	35.96368	39.30119	42.299	45.64289
2.8	26.45646	29.87311	32.91261	36.27216	39.61504	42.61079	45.94533
2.9	26.69541	30.14609	33.20653	36.5801	39.92838	42.92233	46.24813
3	26.93492	30.4191	33.50009	36.88744	40.24112	43.23355	46.5512
3.1	27.17492	30.69205	33.7932	37.19411	40.55321	43.54437	46.85444
3.2	27.41533	30.96486	34.0858	37.50004	40.86458	43.85472	47.15776
3.3	27.65609	31.23747	34.37783	37.80517	41.17517	44.16454	47.46106
3.4	27.89709	31.50978	34.66918	38.10943	41.48492	44.47374	47.76426
3.5	28.13823	31.78165	34.95975	38.41268	41.79367	44.78217	48.06718
3.6	28.37935	32.05295	35.24936	38.71477	42.10129	45.08967	48.3696
3.7	28.62032	32.32351	35.53786	39.01554	42.40758	45.39605	48.67134
3.8	28.86097	32.59316	35.82508	39.31481	42.71238	45.70111	48.97216

3.9	29.10115	32.86174	36.11086	39.61241	43.0155	46.00466	49.27186
4	29.34067	33.12904	36.39498	39.90813	43.31672	46.30648	49.57018
4.1	29.57933	33.39486	36.67722	40.20173	43.61578	46.60627	49.8668
4.2	29.81691	33.65894	36.95733	40.49296	43.91244	46.90378	50.16144
4.3	30.0532	33.92109	37.23509	40.78159	44.20643	47.19872	50.4538
4.4	30.28799	34.18105	37.51025	41.06735	44.4975	47.49083	50.74358
4.5	30.52102	34.43856	37.78254	41.34996	44.78531	47.77976	51.03041
4.6	30.75201	34.69332	38.05162	41.62907	45.06953	48.06514	51.31389
4.7	30.98072	34.94506	38.31723	41.90441	45.34985	48.34666	51.59368
4.8	31.20691	35.19353	38.57911	42.17568	45.62597	48.62399	51.86945
4.9	31.43034	35.43847	38.83698	42.44263	45.89763	48.89687	52.1409
5	31.65077	35.67964	39.0906	42.70499	46.16454	49.16499	52.40771
5.1	31.868	35.91681	39.33972	42.96251	46.42643	49.42807	52.66959
5.2	32.08189	36.14985	39.58423	43.21507	46.68321	49.68601	52.92642
5.3	32.29241	36.37874	39.82411	43.46268	46.93487	49.93882	53.17823
5.4	32.4995	36.60342	40.05932	43.70529	47.1814	50.18649	53.425
5.5	32.70301	36.82376	40.28973	43.9428	47.42268	50.42891	53.66662
5.6	32.90283	37.03965	40.51524	44.1751	47.65862	50.66598	53.903
5.7	33.09882	37.25096	40.73571	44.40207	47.8891	50.89758	54.13402
5.8	33.29087	37.45757	40.95105	44.62362	48.11403	51.12365	54.35961
5.9	33.47887	37.65939	41.16118	44.83968	48.33334	51.3441	54.57969
6	33.66272	37.85633	41.36602	45.05017	48.54699	51.55888	54.79422
6.1	33.84237	38.04837	41.56553	45.25508	48.75494	51.76799	55.00317
6.2	34.01777	38.23545	41.7597	45.4544	48.9572	51.97142	55.20657
6.3	34.1889	38.41759	41.94856	45.64816	49.15383	52.16924	55.40447
6.4	34.35581	38.59487	42.13219	45.83649	49.34495	52.3616	55.59704
6.5	34.51857	38.76738	42.31073	46.01954	49.53076	52.5487	55.78451
6.6	34.67726	38.93523	42.48431	46.19748	49.71143	52.73074	55.96708
6.7	34.83188	39.09848	42.65301	46.3704	49.8871	52.90786	56.14492
6.8	34.98246	39.25718	42.81691	46.53841	50.05786	53.08019	56.31816
6.9	35.12901	39.41134	42.97605	46.70157	50.22381	53.24783	56.48692
7	35.27148	39.56097	43.13044	46.85991	50.38499	53.41081	56.65123
7.1	35.40985	39.70605	43.28009	47.01342	50.54141	53.56917	56.81115
7.2	35.54408	39.84657	43.42498	47.16214	50.6931	53.72295	56.96672
7.3	35.67423	39.9826	43.56522	47.30618	50.84019	53.87229	57.1181
7.4	35.80042	40.11432	43.70103	47.44578	50.98297	54.01748	57.26558
7.5	35.92285	40.24196	43.83266	47.58124	51.12175	54.15888	57.40956
7.6	36.04173	40.3658	43.96042	47.71291	51.2569	54.29689	57.55047
7.7	36.15725	40.48606	44.08459	47.84108	51.38878	54.43187	57.68869
7.8	36.26956	40.60295	44.20539	47.96602	51.51765	54.56411	57.82453
7.9	36.37878	40.71662	44.32302	48.08796	51.64378	54.6939	57.9583
8	36.48505	40.82724	44.43766	48.2071	51.7674	54.82149	58.09026
8.1	36.58851	40.935	44.54954	48.32369	51.88875	54.94714	58.2207
8.2	36.68936	41.04014	44.65892	48.43803	52.00819	55.07123	58.35001
8.3	36.78783	41.14293	44.7661	48.55045	52.12606	55.19413	58.4786
8.4	36.88409	41.24358	44.87136	48.66125	52.24271	55.3162	58.60684

8.5	36.97829	41.3423	44.9749	48.77069	52.35841	55.43774	58.73505
8.6	37.07056	41.43925	45.07692	48.87897	52.47338	55.55898	58.8635
8.7	37.161	41.53456	45.17758	48.98629	52.58785	55.68018	58.99245
8.8	37.2497	41.62836	45.27705	49.09283	52.70202	55.80156	59.12214
8.9	37.33676	41.72079	45.37547	49.19876	52.8161	55.92332	59.2528
9	37.42227	41.81197	45.473	49.30428	52.93027	56.0457	59.38466
9.1	37.50633	41.90203	45.56979	49.40955	53.04474	56.16888	59.51795
9.2	37.58903	41.99109	45.66598	49.51472	53.15967	56.29308	59.65288
9.3	37.67046	42.07927	45.76171	49.61997	53.27526	56.41847	59.78965
9.4	37.75071	42.16668	45.85712	49.72544	53.39166	56.54525	59.92847
9.5	37.82987	42.25344	45.95235	49.83131	53.50907	56.67361	60.06955
9.6	37.90805	42.33969	46.04753	49.9377	53.62764	56.80373	60.21306
9.7	37.98532	42.4255	46.14277	50.04474	53.74748	56.93572	60.35915
9.8	38.06175	42.51096	46.23814	50.15252	53.86871	57.06971	60.50794
9.9	38.13745	42.59619	46.33381	50.26122	53.99152	57.20589	60.65965
10	38.21257	42.68136	46.42994	50.37101	54.1161	57.34449	60.8145
10.1	38.28722	42.76661	46.52669	50.48208	54.24265	57.4857	60.97273
10.2	38.36152	42.85207	46.62421	50.59459	54.37134	57.62972	61.13453
10.3	38.43558	42.93787	46.72263	50.70867	54.50233	57.77672	61.30009
10.4	38.5095	43.02411	46.82206	50.82444	54.63574	57.92683	61.46955
10.5	38.58338	43.11087	46.9226	50.94203	54.7717	58.08017	61.64307
10.6	38.6573	43.19827	47.02436	51.06154	54.91033	58.2369	61.82079
10.7	38.73135	43.28639	47.12743	51.18306	55.05172	58.3971	62.0028
10.8	38.80561	43.37529	47.23186	51.30663	55.19592	58.56082	62.18916
10.9	38.88017	43.46506	47.33773	51.43235	55.34303	58.72816	62.37998
11	38.95515	43.55581	47.44515	51.56033	55.49314	58.89924	62.57539
11.1	39.03065	43.64764	47.55423	51.69067	55.64638	59.07417	62.77549
11.2	39.1068	43.74066	47.66506	51.82346	55.80283	59.25304	62.98042
11.3	39.18369	43.83497	47.77775	51.9588	55.96261	59.43598	63.19027
11.4	39.26146	43.93068	47.89239	52.0968	56.12582	59.62309	63.40517
11.5	39.34017	44.02785	48.00905	52.23751	56.29249	59.81441	63.62518
11.6	39.41989	44.12651	48.12773	52.38092	56.46262	60.00993	63.85026
11.7	39.50069	44.22673	48.24848	52.52706	56.63624	60.20967	64.08045
11.8	39.58264	44.32853	48.3713	52.67593	56.81332	60.41361	64.31573
11.9	39.66576	44.4319	48.49617	52.82748	56.99383	60.6217	64.55604
12	39.75011	44.53687	48.62309	52.98169	57.1777	60.83389	64.80132
12.1	39.83567	44.64338	48.75198	53.13847	57.36485	61.05005	65.05146
12.2	39.92245	44.75141	48.88279	53.29775	57.55518	61.27012	65.30637
12.3	40.01046	44.86095	49.0155	53.45948	57.74865	61.49402	65.56601
12.4	40.09974	44.97201	49.15009	53.62363	57.94522	61.72172	65.83031
12.5	40.19034	45.08461	49.28656	53.7902	58.14486	61.95319	66.09927
12.6	40.28231	45.19875	49.4249	53.95915	58.34753	62.1884	66.37285
12.7	40.3757	45.31446	49.56511	54.13046	58.55321	62.4273	66.65102
12.8	40.47049	45.4317	49.70712	54.30404	58.7618	62.6698	66.93369
12.9	40.56661	45.55034	49.85077	54.47972	58.97309	62.91569	67.22062
13	40.66397	45.67027	49.99594	54.65733	59.18691	63.16475	67.51159

13.1	40.76251	45.79139	50.14249	54.8367	59.40305	63.41677	67.80637
13.2	40.86213	45.91357	50.29024	55.01765	59.62129	63.67153	68.10474
13.3	40.96279	46.03672	50.43911	55.20004	59.8415	63.92885	68.40648
13.4	41.06448	46.16082	50.58902	55.38378	60.06355	64.18862	68.71149
13.5	41.16722	46.28587	50.73998	55.56886	60.28743	64.45081	69.01974
13.6	41.27117	46.41201	50.89211	55.75541	60.51327	64.71555	69.3314
13.7	41.3765	46.5394	51.04558	55.9436	60.74126	64.98306	69.64669
13.8	41.48337	46.66821	51.20054	56.13358	60.97155	65.25353	69.96585
13.9	41.59193	46.79856	51.35712	56.32549	61.20432	65.52714	70.28908
14	41.70229	46.93058	51.51546	56.51947	61.4397	65.80405	70.61657
14.1	41.81454	47.06437	51.67566	56.71565	61.67784	66.08439	70.94848
14.2	41.92873	47.19999	51.83778	56.91407	61.91878	66.36824	71.28489
14.3	42.04479	47.33735	52.00172	57.11463	62.16241	66.65548	71.62569
14.4	42.1626	47.47633	52.16735	57.31718	62.40857	66.94595	71.9707
14.5	42.28205	47.61681	52.33455	57.52158	62.6571	67.23945	72.31975
14.6	42.40304	47.75868	52.50316	57.72766	62.90783	67.53581	72.67263
14.7	42.52547	47.90183	52.6731	57.93531	63.1606	67.83488	73.02918
14.8	42.64925	48.04615	52.8442	58.14436	63.41526	68.13648	73.38922
14.9	42.77427	48.19153	53.01637	58.35469	63.67165	68.44044	73.75256
15	42.90042	48.33786	53.18948	58.56615	63.92961	68.74657	74.11902
15.1	43.0276	48.48501	53.36339	58.77859	64.18896	69.05469	74.4884
15.2	43.15562	48.63281	53.53791	58.99179	64.44947	69.36455	74.8604
15.3	43.2843	48.78107	53.71283	59.20554	64.7109	69.67587	75.23476
15.4	43.41343	48.92958	53.88795	59.41959	64.97298	69.98838	75.61115
15.5	43.54281	49.07814	54.06305	59.63371	65.23544	70.30175	75.9892
15.6	43.67225	49.22654	54.23788	59.84763	65.49796	70.61565	76.36856
15.7	43.80162	49.37463	54.4123	60.06116	65.76035	70.92986	76.74898
15.8	43.93089	49.52239	54.58625	60.27427	66.02254	71.24429	77.13036
15.9	44.06003	49.6698	54.75974	60.4869	66.28449	71.55888	77.51262
16	44.18901	49.81682	54.9327	60.69902	66.54613	71.87356	77.89568
16.1	44.31775	49.96336	55.10506	60.91051	66.80733	72.18818	78.27937
16.2	44.44627	50.10948	55.27684	61.12143	67.06815	72.5028	78.66377
16.3	44.57464	50.25522	55.44813	61.33183	67.32865	72.81752	79.049
16.4	44.70287	50.4006	55.61893	61.54176	67.58889	73.13239	79.43513
16.5	44.831	50.54569	55.78931	61.75127	67.84893	73.44746	79.82226
16.6	44.9591	50.69055	55.95935	61.96046	68.10888	73.76289	80.2105
16.7	45.08723	50.83526	56.12915	62.16943	68.36884	74.07878	80.60002
16.8	45.21541	50.97985	56.29873	62.37821	68.62886	74.39518	80.99087
16.9	45.34364	51.12434	56.46811	62.58683	68.88896	74.71211	81.38309
17	45.47194	51.26874	56.63732	62.79531	69.14919	75.02963	81.77674
17.1	45.60031	51.41307	56.80637	63.00368	69.40954	75.34776	82.17184
17.2	45.72876	51.55733	56.97528	63.21194	69.67005	75.66651	82.56846
17.3	45.85735	51.7016	57.14413	63.4202	69.93082	75.98602	82.96673
17.4	45.98612	51.84593	57.31296	63.62849	70.19191	76.30637	83.36676
17.5	46.11512	51.99036	57.48183	63.8369	70.45341	76.62764	83.76868
17.6	46.24439	52.13493	57.65078	64.04544	70.71534	76.94989	84.17258

17.7	46.37393	52.27962	57.81978	64.2541	70.9777	77.27312	84.57848
17.8	46.50373	52.42443	57.98882	64.46286	71.24046	77.59733	84.98639
17.9	46.6338	52.56934	58.15786	64.67167	71.50357	77.92248	85.39632
18	46.7641	52.7143	58.32685	64.88049	71.76701	78.24853	85.80828
18.1	46.89464	52.85931	58.49579	65.08928	72.03074	78.57549	86.22227
18.17	46.98615	52.96083	58.614	65.23542	72.21552	78.80489	86.5133