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MICROALBUMINURIA -AN EARLY BIOMARKER OF CARDIOVASCULAR RISK IN COPD PATIENTS

Biochemistry

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KEYWORDS

INTRODUCTION :

Chronic obstructive pulmonary disease (COPD) - a group of progressive lung disease characterized by chronic obstruction of lung air flow that interferes with normal breathing . The term COPD includes both chronic bronchitis and emphysema. The disease is currently defined by post- bronchodilator spirometric forced expiratory volume in 1s (FEV1) / forced vital capacity (FEC) < 0.70 [15].

According to recently published article there were 384 million cases of COPD in 2010, which leads to a global prevalence of 11.7 percent. In India the prevalence of COPD ranges from 2-22% in men & 1.2 – 19 % in women.

COPD is associated with an abnormal inflammatory response in lungs several cytokines and inflammatory mediators have been implicated, but the link between COPD and its systemic expressions are not well understood [(1),(2)]

COPD will become the third leading cause of death by 2020. Cardiovascular disease is a major cause of mortality in COPD, particularly in patients with mild to moderate severity [(3)(4)(5)]. The widespread use of sensitive diagnostic test like ultrasound scan and CT scan are good options. However, because of high prevalence of COPD, these tools may not always be practical in general population for both logistic and economical reasons.

The discovery of biomarkers will help to identify the cardiovascular risk in patients with COPD at earliest, so that we can individualize the treatment. Ideally biomarker should be inexpensive, noninvasive and easily assessable [(2)]

Microalbuminuria (MAB) is a sensitive marker of cardiovascular risk. MAB is believed to reflect a state of generalized endothelial dysfunction [(6)]. A limited number of studies have evaluated the presence of MAB in patients with COPD, mostly during exacerbations [(7)(8)(9)]. In those studies, the influence of cardiovascular risk factors was not considered. MAB is elevated in patients with COPD independently of other cardiovascular risk factors. We hypothesize that MAB levels as an early marker of cardiovascular risk in COPD patients.

Review Of Literature:

Chronic obstructive pulmonary disease (COPD):

COPD is defined as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases.

Related diagnosis include chronic bronchitis (cough and sputum for at least 3 consecutive months in each of 2 consecutive years) and Emphysema (abnormal permanent enlargement of airspaces distal to the terminal bronchioles , accompanied by destruction of their walls and without obvious fibrosis[(10)].

Risk Factors :[(10)]

Environmental Factors

- Tobacco smoke (95%)
- Restricted lung growth in children due to maternal smoking
- Indoor air pollution –cooking with biomass
- Occupational exposure – coal dust
- Low socioeconomic status
- Recurrent infections – adenovirus , HIV
- Low birth weight

Host Factors

- Antitrypsin deficiency
- Airway hypersensitivity
- Chronic IV drug use

Pathogenesis Of Copd: [(11)]

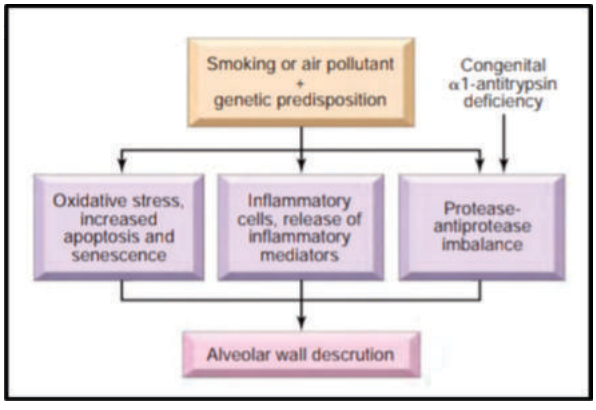
Emphysema and chronic Bronchitis are often clinically grouped together and referred as COPD, Since majority of patients share the features of both.

Emphysema is characterized by irreversible enlargement of air spaces distal to terminal bronchiole, accompanied by destruction of their walls without obvious fibrosis

Types Of Emhysema

1. Centriacinar emphysema – mostly seen
2. Panacinar emphysema – associated with Alpha 1 antitrypsin deficiency
3. Distal acinar emphysema
4. Irregular emphysema

Inhaled cigarette smoke and other noxious particles cause lung damage and inflammation which results in parenchymal destruction and airway disease .



Chronic bronchitis is characterized with persistent cough with sputum production for atleast 3 months in atleast 2 consecutive years with absence of any other identifiable cause

1. Earliest feature of chronic bronchitis - Mucus hypersecretion and ciliary dysfunction

- Normal pseudostratified ciliated epithelium of the airway is replaced by goblet cells, and in the later stages by squamous metaplasia
- Enlargement of mucous glands – mucus production that is abnormal in quality and increased in quantity
- Cilia that is responsible for mucus clearance is disrupted

2. Fibrosis and airflow limitation

- Smaller airways (<2 mm in diameter) accumulate mesenchymal cells, which produce collagenous extracellular matrix → fibrosis and narrowing

- Mucus hypersecretion also contributes to airflow limitation

3. Gas-Exchange abnormalities
- Occurs in advanced disease and is characterized by arterial hypoxemia ($\uparrow O_2$) with or without hypercapnia ($\uparrow CO_2$).
- Abnormal gas exchange due to abnormal ventilation-perfusion (V/Q) ratio

4. Pulmonary Hypertension
- Also occurs in advanced disease, normally after development of severe gas exchange abnormalities.
- Contributing factors: vasoconstriction (mostly hypoxic origin), endothelial dysfunction, remodeling of pulmonary arteries and destruction of the pulmonary capillary bed, which may lead to right ventricular hypertrophy and corpulmonale (right heart failure)

Clinical Features
Patients often complaint of difficulty in breathing may be associated with cough and expectoration. The small number of patients presents with cough as a chief complain which often confuses with asthma .Classically the patients with emphysema is barrel chested and dyspneic with prolonged expiration , sits forward and breath through pursed lips. Long standing severe cases leads to corpulmonale and cardiac failure.

AIM:
To consider Microalbuminuria (MAB) levels as a early biomarker of cardiovascular risk.

OBJECTIVES :
1 To estimate the MAB level in stable male COPD patients and healthy control male smokers
2 To assess correlation between smoking index and urine albumin creatinine ratio in stable male COPD patients.

MATERIALS :
- **Study Design**: Comparative cross-sectional study
- **Intervention** : None
- **Setting**: Department of Biochemistry and Departments of Thoracic And general Medicine in a tertiary care hospital in South India.

Study Population :
Cases (Group 2): stable male COPD patients including inpatients and outpatients in the department of thoracic medicine.

Control(Group 1) : Age matched healthy male control smokers

Inclusion criteria:
- **Cases :** Age: 35 – 70 Years male
- **Controls:** male Smokers for more than 10 years without any air flow obstruction

Exclusion Criteria :
Controls and Patients with history of any renal disease, Cardiovascular disease, uncontrolled comorbidites such as malignancy ,Asthma or other confounding diseases, patients with history of diabetes, hypertension and dyslipidemia.

Sample Size
Sample size $= \frac{Z^2 SD^2}{L^2}$
L(absolute precision)
SD(standard deviation)
Z(constant)
By substituting the values in the given formulae,
A sample size of 180 participants with 90 cases and 90 control males between 35 – 65 age groups will be included in the study.

Expected duration of study :
2 Months

METHODS:
Known male COPD Patients attending Thoracic Medicine OP as well as inpatients will be randomly selected as per predetermined randomization criteria. Among them, those who fit in the inclusion criteria and willing to participate in the study will be recruited. Age matched healthy male control smokers attending the master health checkup will be included in the study. Informed consent will be obtained from both the participants.

On recruitment to the study, fasting blood and spot urine samples will be collected simultaneously while at rest.

Investigations:
- Urine albumin concentration will be determined by standard turbidimetric method.
- Serum and urine creatinine concentrations will be analyzed using Jaffe reaction and quantified by photometric method.
- Urine albumin excretion will be determined as urine albumin (mg) to creatinine (g) ratio (UACR) in the morning urine sample.
- Serum levels of glucose will be determined by Glucose oxidase – peroxidase method (GOD-POD method)
- Serum Triglycerides by GPO-POD method and serum cholesterol by CHOD-POD method will be determined in a fully automated analyzer.

If Urine albumin to creatinine ratio ≥20 mg/g, then it is called as Microalbuminuria.

OBSERVATION AND RESULTS:
This study was done to estimate the Microalbuminuria level in stable male COPD patients and healthy control male smokers was done in 180 subjects , of which 90 with known COPD were taken as cases and 90 male smokers without COPD were taken as controls.

Statistical Analysis:
All data were entered in computer software statistical package for social sciences (SPSS) version 16.0. Data were summarized as mean and standard deviation for normally distributed variable; 95% confidence intervals were estimated. Student t-test was used to compare the patient group with control group.

P value < 0.05 indicates statistical significance. Pearson's correlation was used to find the association between the variables.

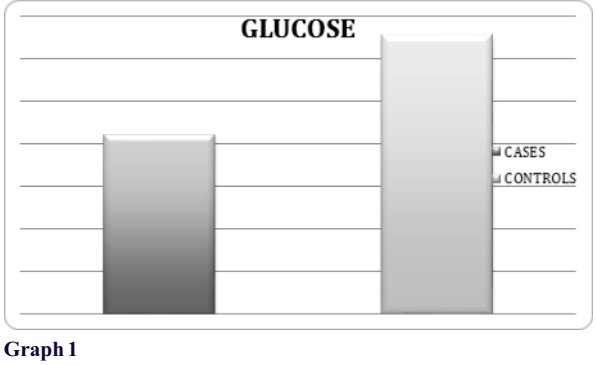
Table: 1 Age distribution between study populations

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Age (years)	55.87± 8.13	55.3±10.71	0.69	Not significant

TABLE 1 – Shows age distribution into study and control group . It shows no significant difference in age between two groups. This study groups are comparable.

Table 2:Comparison of Glucose levels between cases and control groups

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Glucose mg/dl	84.18 ±40.25	131.29 ± 36.03	0.3	Not significant

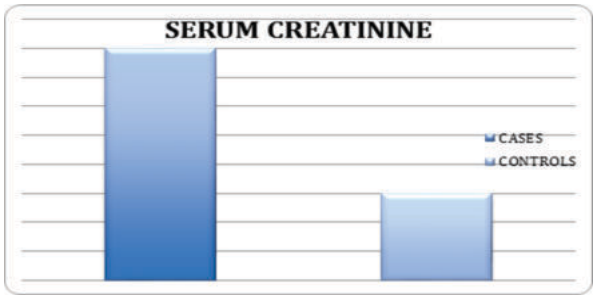


Graph 1

Graph 1 and Table 2: shows the Glucose levels in case group and control group . These data shows there is no statistically significant difference in Glucose levels between case and control groups.

Table: 3 -Comparison of Serum creatinine levels between case and control groups.

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Serum creatinine mg/dl	1.10±0.43	1.05 ±0.44	0.82	Not significant

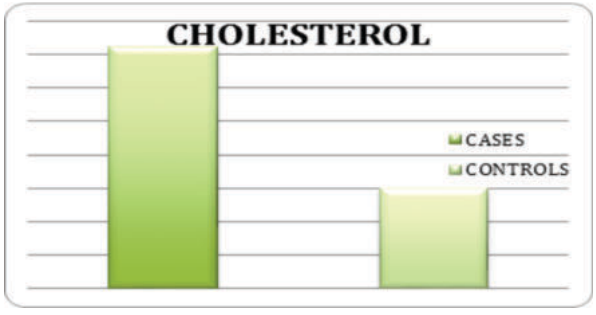


Graph 2

Graph 2 and Table 3 : shows the Serum creatinine levels in case group and control group . These data shows there is no statistical significance in Serum creatinine levels between case and control groups.

Table 4: Comparison of Cholesterol levels between cases and control groups

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Cholesterol mg/dl	144.04 ±33.27	143.20 ±36.25	0.41	Not significant

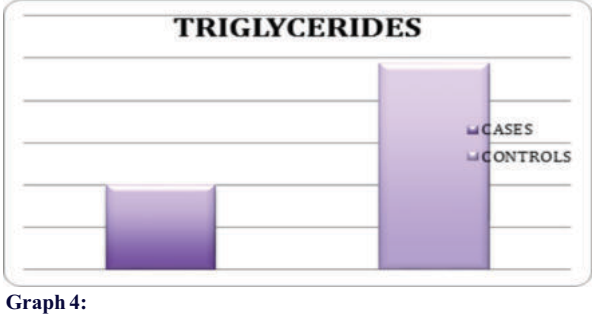


Graph 3

Graph 3 and Table 4: shows the Cholesterol levels in case group and control group . These data shows there is no statistically significant difference in cholesterol levels between case and control groups.

Table 5: Comparison Of Triglyceride Levels Between Cases And Control Groups

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Triglyceride mg/dl	109.80 ±41.80	109.94 ±39.42	0.58	Not significant

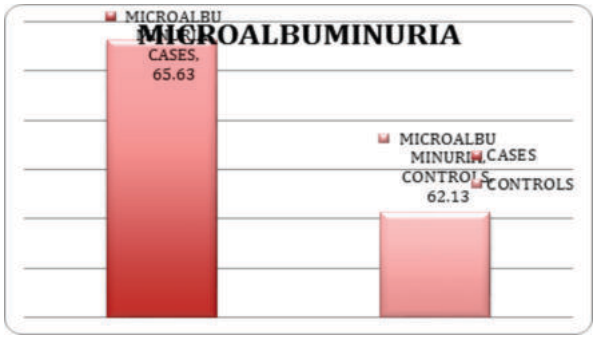


Graph 4:

Graph 4 and Table 5 : shows the Triglycerides levels in case group and control group . These data shows there is no statistically significant difference in Triglyceride levels between case and control groups.

Table 6: Comparison of Microalbuminuria levels between cases and control groups

Parameter	Group 1 (Cases) N=90 Mean ± SD	Group 2 (control) N=90 Mean± SD	P value	Statistical significance
Microalbuminuria mg/g	65.63± 62.85	62.13 ±48.85	0.01	Very significant



Graph 5:

Graph 5 and Table 6: shows the Microalbuminuria levels in case group and control group . These data shows there is statistically significant difference in Microalbuminuria levels between case and control groups.

Table 7: Pearson's correlation between Smoking index and Microalbuminuria in COPD patients.

Parameter	Group 1 Cases N=90	Statistical analysis
r value	0.78	Strong correlation
P value	0.001	Highly Significant

r value = > 0.7 strong correlation
r value =0.3 to 0.7 Moderate correlation
r value = < 0.3 weak correlation
r value = 0 to < 0.1 NO correlation

DISCUSSION:

This study was done to find the MAB level in stable male COPD patients and healthy control male smokers and to assess correlation between smoking index and urine albumin creatinine ratio in stable male COPD patients.

So in this study urine albumin creatinine ratio is measured along with serum glucose, creatinine, cholesterol and triglycerides to exclude the other comorbid factors in the subjects.

Microalbuminuria (MAB) is a sensitive marker of cardiovascular risk. MAB is believed to reflect a state of generalized endothelial dysfunction[6].

In this study , Microalbuminuria(MAB) levels between COPD patients and controls were significant since P value is < 0.05 which is consistent with the findings of studies by Bulcun, Emel et al in turkey[12] and Khalid Mehmood* and Fayaz Ahmad Sof in Kashmir[13] .

In this study, the relation between smoking index and Micro albuminuria are compared in COPD patients and results shows strong positive correlation since r value > 0.7 was similar to findings of R.K.Gupta , V.D.Maheshwari et al. [14]

We have also found an independent association between Microalbuminuria and COPD, excluding other diseases causing endothelial disfunction like Diabetes, hypertension, dyslipidemia , renal disease and asthma.

CONCLUSION :

In our study, Microalbuminuria (MAB) levels are increased in COPD patients than healthy male control smokers and There is positive

correlation between smoking index and Microalbuminuria in stable male COPD patients.

Since Microalbumiuria(MAB) is considered as a marker of endothelial disfunction and cardiovascular risk is the most common cause of mortality in COPD patients, elevated MAB levels in COPD patients can be considered as a early biomarker of cardiovascular risk excluding the other comorbid factors.

So, screening for MAB in COPD patient earlier will prevent morbidity and mortality of COPD patient.

Summary:
COPD is the third leading cause of mortality worldwide. Since cardiovascular risk is the major cause of mortality in COPD patients , the levels of Microalbuminuria which is a marker of endothelial disfunction is estimated in COPD patients and healthy smokers. Significant increase in Microalbuminuria levels is noted in COPD patients than in age matched healthy male smokers. The positive correlation between smoking index and Microalbuminuria in COPD patients have been found.

Data Collection Sheet :
Cases:

S.NO	AGE	GLUCOSE mg/dl	SERUM CREATININE mg/dl	CHOLESTEROL mg/dl	TRIGLYCERIDES mg/dl	MAB g/mg	SMOKING INDEX Pack years
1	62	95	0.80	169	107.00	29.90	110
2	54	161	1.00	188	177.00	3.00	70
3	48	55	0.90	119	79.00	15.00	90
4	59	55	0.90	159	116.00	87.90	150
5	65	79	1.20	143	149.00	5.00	75
6	62	71	1.00	140	73.00	13.50	85
7	64	63	1.00	101	68.00	21.05	108
8	62	57	0.90	157	133.00	137.09	156
9	55	79	0.90	153	70.00	35.00	128
10	65	110	1.00	170	184.00	149.20	172
11	62	69	1.00	131	146.00	128.00	160
12	40	136	0.80	116	64.00	33.67	124
13	60	108	0.80	117	62.00	3.00	68
14	62	42	0.90	129	90.00	31.40	120
15	63	100	1.00	132	101.00	4.50	70
16	65	68	1.20	116	69.00	0	60
17	62	178	1.20	199	115.00	182.19	204
18	55	125	1.20	101	64.00	124.26	156
19	57	68	0.90	185	200.00	181.48	192
20	54	67	1.00	140	69.00	9.80	80
21	63	68	0.90	162	64.00	33.33	120
22	52	74	0.80	200	67.00	23.40	108
23	61	51	0.90	113	67.00	18.40	100
24	57	86	0.80	130	186.00	24.40	135
25	65	52	0.80	106	97.00	30.83	148
26	61	146	1.20	200	200.00	33.33	154
27	45	75	0.90	142	112.00	29.47	144
28	62	69	1.30	200	95.00	12.73	80
29	60	70	0.90	118	187.00	45.35	168
30	65	141	1.10	168	122.00	8.60	45
31	65	52	1.00	204	92.00	53.00	178
32	55	66	0.80	119	69.00	175.00	190
33	62	101	0.80	142	65.00	37.27	129
34	61	73	1.20	136	56.00	46.30	135
35	48	160	0.80	162	172.00	233.33	108
36	59	90	0.90	141	91.00	10.00	70
37	59	121	1.20	153	76.00	139.67	170
38	47	60	0.90	129	101.00	211.11	230
39	35	84	0.90	106	86.00	10.80	96
40	61	124	1.10	106	60.00	8.70	95
41	62	81	0.80	155	98.00	55.60	130
42	55	63	0.60	129	87.00	66.40	138
43	63	60	1.00	66	89.00	200.70	210
44	53	65	0.80	170	171.00	50.60	156
45	55	85	1.20	152	149.00	41.67	150
46	60	70	0.80	167	63.00	70.33	160
47	51	77	0.90	131	82.00	20.93	70
48	39	68	0.70	159	142.00	82.40	168
49	54	166	2.80	148	103.00	219.70	220
50	47	101	0.70	65	57.00	279.40	230
51	57	50	1.20	89	159.00	9.80	100
52	58	42	1.60	109	95.00	145.90	175
53	65	47	0.50	231	207.00	60.20	162
54	65	66	0.90	154	60.00	56.67	160
55	62	58	0.80	160	116.00	84.00	174
56	64	53	0.90	84	64.00	111.11	260
57	57	52	1.70	138	134.00	6.00	90
58	48	130	0.60	115	128.00	2.78	75
59	64	60	0.90	144	120.00	45.60	132
60	53	67	1.00	172	123.00	26.00	124
61	55	57	0.90	189	114.00	121.40	189
62	63	60	0.80	160	184.00	6.20	96
63	42	52	0.70	152	74.00	89.00	156
64	62	45	0.90	185	82.00	5.90	84
65	63	79	1.10	200	171.00	54.39	144
66	35	52	1.00	124	77.00	123.70	150
67	44	237	0.80	111	101.00	29.00	135
68	46	53	1.90	122	93.00	57.53	175
69	58	78	1.90	148	86.00	143.00	195
70	58	36	1.60	100	70.00	28.00	130
71	37	45	0.80	120	171.00	3.50	100
72	35	64	1.00	163	172.00	110.80	178
73	63	40	1.70	169	65.00	76.90	164
74	63	200	1.10	199	141.00	46.00	96
75	54	53	1.60	189	135.00	183.72	210
76	60	66	0.90	184	101.00	2.60	98
77	53	42	0.80	127	153.00	47.70	156
78	55	209	1.70	117	133.00	64.80	80
79	37	54	1.60	167	189.00	132.14	190
80	60	72	1.10	127	96.00	60.50	160
81	42	87	1.20	133	97.00	68.91	150
82	50	76	1.00	140	76.00	45.70	145
83	56	110	2.70	147	114.00	75.33	178
84	52	169	1.50	185	72.00	26.70	96
85	56	100	2.90	95	65.00	8.40	96
86	62	76	1.80	105	156.00	4.50	72
87	63	89	1.20	145	97.00	105.20	174
88	51	98	1.40	135	133.00	59.43	156
89	57	78	1.40	180	144.00	36.70	138
90	45	89	1.20	106	72.00	73.69	160

Controls:

SL NO	AGE years	GLUCOSE mg/dl	SERUM CREATININE mg/dl	CHOLESTEROL mg/dl	TRIGLYCERIDES mg/dl	MICROALBUMINURIA mg/g
1	37	100	0.80	130	189.00	2.80
2	42	174	1.00	115	77.00	111.56
3	57	135	0.90	120	133.00	39.39
4	56	140	0.60	133	79.00	190.63
5	65	129	1.40	152	76.00	13.00
6	57	167	1.30	117	150.00	22.50
7	52	96	0.60	202	117.00	61.56
8	52	102	1.40	99	82.00	36.00
9	54	102	0.90	189	179.00	103.18
10	42	172	0.90	139	108.00	125.00
11	54	158	0.60	170	70.00	90.13
12	35	128	0.80	189	210.00	96.57
13	60	133	1.10	123	64.00	45.24
14	51	90	0.70	162	114.00	122.37
15	65	103	1.00	144	71.00	1.00
16	61	94	1.10	145	100.00	180.50
17	48	116	1.20	100	94.00	124.00
18	61	120	0.80	158	65.00	176.84
19	44	114	1.40	156	67.00	9.40
20	51	210	2.30	171	148.00	42.43
21	65	110	1.50	200	65.00	45.77
22	60	120	1.30	118	66.00	88.28
23	61	94	1.90	143	65.00	48.06

24	60	121	0.80	120	187.00	58.62
25	60	185	0.90	142	98.00	81.00
26	53	107	0.70	156	200.00	90.48
27	45	186	1.20	129	113.00	62.73
28	62	93	0.70	116	96.00	15.87
29	56	89	1.30	108	155.00	94.49
30	65	83	0.90	176	123.00	15.59
31	37	168	1.10	166	93.00	4.50
32	62	130	1.30	209	72.00	19.44
33	55	101	1.40	133	75.00	90.91
34	50	139	0.90	200	65.00	5.00
35	62	106	0.40	108	172.00	54.53
36	65	130	0.9	198	92.00	51.56
37	51	91	1.6	199	78.00	110.00
38	64	124	0.6	119	110.00	9.76
39	40	109	1.6	169	87.00	28.90
40	64	113	0.6	145	63.00	16.47
41	64	96	1.2	67	160.00	8.59
42	42	91	0.9	150	98.00	150.00
43	37	118	0.8	158	203.00	53.33
44	61	138	0.9	134	65.00	25.71
45	42	129	1.6	168	130.00	94.00
46	48	200	0.7	154	67.00	56.00
47	63	202	1.10	176	133.00	23.00
48	54	62	0.70	65	129.00	11.00
49	55	102	1.00	130	123.00	23.80
50	53	164	0.80	106	152.00	30.30
51	63	150	1.60	154	115.00	43.55
52	53	152	1.40	170	187.00	76.15
53	45	190	0.60	129	75.00	99.80
54	46	162	1.20	164	87.00	30.63
55	54	132	0.70	189	170.00	139.59
56	47	131	0.50	203	76.00	17.14
57	62	82	0.30	110	100.00	20.00
58	63	158	1.50	16	98.00	76.00
59	62	129	0.80	130	85.00	18.52
60	57	148	1.20	119	74.00	69.39
61	58	180	2.10	90	187.00	52.31
62	62	109	1.00	108	113.00	200.50
63	39	191	0.60	214	76.00	49.00
64	48	151	0.50	156	170.00	3.20
65	63	143	1.80	161	75.00	200.00
66	63	106	0.40	87	96.00	99.74
67	62	129	1.10	134	87.00	6.80
68	62	185	0.90	116	98.00	155.07
69	47	180	1.30	145	109.00	71.14
70	65	116	2.20	177	171.00	45.80
71	54	161	1.20	143	125.00	56.20
72	58	148	0.20	167	145.00	38.49
73	63	216	1.10	199	98.00	51.46
74	55	131	1.50	176	75.00	23.50
75	63	112	0.70	156	130.00	73.75
76	62	161	0.60	134	67.00	9.00
77	63	124	0.60	120	89.00	46.45
78	55	128	1.70	113	76.00	85.31
79	65	122	0.80	132	64.00	70.26
80	58	192	0.90	154	109.00	64.68
81	59	106	2.20	160	104.00	36.88
82	57	126	0.80	145	114.00	9.00
83	35	72	0.70	172	154.00	112.80
84	62	93	1.20	67	87.00	67.37
85	62	70	0.70	132	110.00	78.92
86	65	190	1.50	156	132.00	67.62
87	55	96	1.00	134	156.00	11.67
88	55	183	1.70	148	109.00	105.00
89	35	72	0.80	165	98.00	10.15
90	57	105	0.70	67	76.00	37.00

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