Determinants of Time-to-Death of Chronic Lymphocytic Leukemia Patients at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia

Cancer Informatics
Volume 22: 1–5
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DOI: 10.1177/11769351231183849
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ABSTRACT

BACKGROUND: Leukemia is a group of cancers that usually begin in the bone marrow and results in a large number of abnormal white blood cells. Chronic Lymphocytic Leukemia is the most prevalent leukemia in Western countries, with an estimated incidence rate of less than 1 to 5.5 per 100 000 people, and average age at diagnosis of 64 to 72 years. It is more common in men among Chronic Lymphocytic Leukemia patients in Ethiopia's hospitals at Felege Hiwot Referal Hospital.

METHODS: A retrospective cohort research design was employed to acquire critical information from patients' medical records in order to achieve the study's purpose. The study comprised the medical records of 312 Chronic Lymphocytic Leukemia who were followed from January 1, 2018 to December 31, 2020. A Cox proportional hazard model was used to determine the risk factors for time to death in Chronic Lymphocytic Leukemia patients.

RESULTS: Accordingly the Cox proportional hazard model, age (Hazard Ratio = 11.36; $P < .001$), sex of male (Hazard Ratio = 1.04; $P = .004$), married status (Hazard Ratio = 0.03; $P = .003$), medium stages of Chronic Lymphocytic Leukemia (Hazard Ratio = 1.29; $P = .024$), high stages of Chronic Lymphocytic Leukemia (Hazard Ratio = 1.99; $P < .001$), presence of anemia (Hazard Ratio = 0.09; $P = .005$), platelets (Hazard Ratio = 2.11; $P = .007$), hemoglobin (Hazard Ratio = 0.02; $P < .001$), lymphocytes (Hazard Ratio = 0.29; $P = .006$), red blood cell (Hazard Ratio = 0.02; $P < .001$), which patients with Chronic Lymphocytic Leukemia had a significant relationship with time to death.

CONCLUSIONS: Age, sex, Chronic Lymphocytic Leukemia stage, anemia, platelets, hemoglobin, lymphocytes, and red blood cells were all statistically significant determinants in the time to death of Chronic Lymphocytic Leukemia patients, according to the data. As a result, healthcare providers should pay particular attention to and emphasize the identified characteristics, as well as provide frequent counseling on how to enhance the health of Chronic Lymphocytic Leukemia patients.

KEYWORDS: Time to death, Chronic Lymphocytic Leukemia, Cox proportional hazard model

RECEIVED: April 1, 2022. **ACCEPTED:** June 6, 2023.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Leukemia is a group of cancers that usually begin in the bone marrow and results in a large number of abnormal white blood cells. In 2018, it is anticipated that 437.0 thousand new cases of leukemia were diagnosed worldwide, with 309.0 thousand cancer deaths.[1] Pathogenesis, origin, incidence, and prognosis differ among the kinds of leukemia. Mature cells, such as those seen in Chronic Lymphocytic Leukemia, multiline age precursor cells, such as those found in acute leukemia, or both precursor and mature cells, as in chronic myeloid leukemia, may be the predominant leukemia cells.[2]

Chronic Lymphocytic Leukemia is a clonal lymphoproliferative condition of *B*-cells with a malfunctioning programed cell death system (apoptosis). The malignancy has a wide range of outcomes, with some patients requiring just supportive care for long-term survival, while others are plagued by progressing disease with frequently fatal consequences. Chronic lymphocytic leukemia is the most prevalent leukemia in Western countries, with an estimated incidence rate of less than 1 to 5.5 per 100 000 people, with a typical age at diagnosis is 64 to 72 years, and men are more likely to be diagnosed.[3]

Atypical increase of immunologically incompetent cells in the blood, bone marrow, lymph nodes, and spleen characterizes chronic lymphocytic leukemia, a common adult leukemia. In Western countries, chronic lymphocytic leukemia accounts for (25-30) % of all leukemia occurrences, with over 100 000 incidence cases, and over 40 000 mortality cases in 2019.[4] Chronic Lymphocytic Leukemia incidence climbs exponentially with age, reaching a peak in older populations, according to epidemiological studies.[5] The incidence of Chronic Lymphocytic Leukemia is approximately 2 times higher in males than that in females.[6,7] In addition, makeable geographical disparities in

Chronic Lymphocytic Leukemia incidence instances were discovered. Chronic Lymphocytic Leukemia is the most common adult leukemia in Western countries, yet it is uncommon in Asia, even among Asian immigrants to the Western hemisphere.[7,8]

Chronic Lymphocytic Leukemia is continuing on the rise in both developing and developed countries, with varying survival rates depending on medical conditions and economic situations.[9] In the early 2000s, epidemiological research in the United States revealed an alarmingly rising burden, as well as linked incidence and mortality.[10] However, there has been little substantial research on the global burden of Chronic Lymphocytic Leukemia. Furthermore, as a result of recent economic and technological advancements, the distribution, and patterns of Chronic Lymphocytic Leukemia burden have shifted dramatically. The current study on the rapidly growing Chronic Lymphocytic Leukemia burden at a global level is necessary in order to undertake a better assessment of Chronic Lymphocytic Leukemia in public health in order to facilitate clinical policy-making and rational healthcare resource allocation. As a result, the goal of this research was to investigate characteristics that influence the time to death of Chronic Lymphocytic Leukemia patients at Felege Hiwot Referal Hospital in Bahir Dar, Ethiopia.

Method and Material

Study area, period, and design

The study was conducted at Felege Hiwot Referal Hospital, Bahir Dar, North West Ethiopia. Bahir Dar is the capital of Amhara National Regional State. It is located 563-kilo meter far from Addis Ababa, the capital city of Ethiopia, Felege Hiwot Referal Hospital is a referral hospital, and one of the oldest hospitals in Ethiopia, Felege Hiwot Referal Hospital officially commenced its function in 1963 Ethiopian calendar and currently, it delivers health care services to medical, surgical, gynecological, and orthopedic, intensive care units, pediatrics, and ophthalmological wards. Felege Hiwot Referal Hospital delivers health services to their dependents/patients as well as public patients referred by other hospitals and clinics. It conducted a retrospective cohort study design throughout the follow-up time of Chronic Lymphocytic Leukemia patients from 1st January 2018 to 31st December 2020.

Data sources and population

The individuals with chronic lymphocytic leukemia served as the study's population. The information was gathered from the medical records of patients with chronic lymphocytic leukemia who were treated at the hospital between January 2018 and December 2020. The information was taken from the patient's chart, which comprises socio-demographic, and clinical data on all chronic lymphocytic leukemia patients who are being followed up on. As a result, the data used in this inquiry was secondary. The study included patients who had at least 2 follow-up appointments. Patients who had only 1 visit time, therefore the patients not include study.

Quality of data measurement

The data gathering tool was pretested before to the actual data collection to assure data quality. Pre-testing is the process of determining the validity, reliability, practicability, and sensitivity of a tool before it is used to gather data. The completeness and consistency of questions linked to secondary data were checked and pretested on 30 sample data after receiving feedback from the pilot test, and suitable improvements were made. Every day, the data was cleansed, and the data collectors were given rapid feedback.

Sample size determination

To produce statistically significant results, the surviving sample size determination formula was derived as follows[11]:

$$\mathrm{d} = \frac{4[Z_{\frac{\alpha}{2}} + Z_{\beta}]^2}{\theta_R^2}$$

Where

$$\varphi_R = unknown\ hazard\ ratio = 1.6$$

$$\frac{Z0.05}{2} = 1.96\ and\ \beta = 0.1\ which\ is\ 1.28$$

d = Expected number of deaths of Chronic Lymphocytic Leukemia patients

$S_{stage(III-IV)}(t)$—Expected survival rate for the coming specified time to (National Cancer Institute stage III-IV).

$S_{stage(0-II)}(t)$ – The survival rate of stages (National Cancer Institute stage 0-II).

The required total number of Time-To Death in a survival study n was determined as:

The probability of death was calculated as follows:

$$pr(d) = 1 - \frac{1}{6}\left(\bar{S}(t) + 4\bar{S}\left(\frac{1}{2}(t+a)\right) + \bar{S}(t+a)\right)$$

$$\mathrm{d} = \frac{4[Z_{\frac{\alpha}{2}} + Z_{\beta}]^2}{\log(\psi_R)} = \frac{4[1.96+1.28]^2}{\log(\psi_R)} = \frac{4\left[10.51\right]}{\log(1.6)} = \frac{41.99}{\log(1.6)} = 205.72$$

$$pr(default) = 1 - \frac{1}{6}\left(\bar{S}(t) + 4\bar{S}\left(\frac{1}{2}(t+a)\right) + \bar{S}(t+a)\right)$$

$$where\ \bar{S}(t) = \frac{S_{stage(0-II)}(t) + S_{stage(III-IV)}(t)}{2}$$

$$\bar{S}(65) = 0.74, \bar{S}\left(0.5(65+144)\right) = \bar{S}(108) = 0.69, \bar{S}(216) = 0.61$$

$$pr(default) = 1 - \frac{1}{6}(0.74 + 0.69 + 0.61)$$

$pr\left(default\right) = 1 - 0.34 = 0.66,$ Therefore, $n = \frac{\mathrm{d}}{pr\left(default\right)}$ $= \frac{205.72}{0.66} = 311.69 \cong 312,$ Patients with Chronic Lymphocytic Leukemia were chosen using a systematic random sample procedure based on their unique identifying number, and data was collected retrospectively from the time 1st January 2018 to 31st December 2020[12]

Response variable

Survival outcome—time to death under follow-up for Chronic Lymphocytic Leukemia patients. In this study, patients' death by other causes, loss to follow, or transferring to other hospitals were considered censoring.

The explanatory/ independent variables.

The following is a list of the independent variables.

Sex of the respondent (Female = 0; Male = 1)

Residence of the place (Urban = 0; Rural = 1)

Age (is a continuous variable)

Level of educational (0 = illiterate; 1 = literate)

Marital status (unmarried = 0, married = 1)

Platelet measured in platelet count $\times 10^3 / \mu L$ (continuous variable).

Hemoglobin is measured in g / dL (continuous variable).

Hematocrit is a measured in percent (continuous variable).

Lymphocyte (continuous variable):- measured in number/μL

Red blood cell (continuous variable):- measured in count $\times 10^6 / \mu L$

Chronic Lymphocytic Leukemia Stage (low = 0, medium = 1, and high = 2)

Anemia of presence (no = 0; yes = 1)

Statistical analysis

Statistical Package for Social Science program version 23.0 was used to enter the data, which was then exported to *R* statistical software version 4.0.3.

The descriptive statistics were produced to investigate all of the study's variables. To determine the link between time to death and independent variables, a Cox proportional hazard model was used. If the *P*-value was less than .05, the results were considered statistically significant.

Results

Characteristics of the participants in the study

The survival endpoint of interest is death from chronic lymphocytic leukemia treatment. In this study, patients' death by another case, loss to follow, or transferring to other hospitals were considered censored. A total of 312 chronic lymphocytic leukemia patients were included and 101(32.4%) were events or deaths, whereas 211(67.6%) were censored, or treated at the end of the study period. Twenty-nine(28.7%) female patients and 72(71.3%) patients were male patients were deaths (Tables 1 and 2).

Table 1. Chronic lymphocytic leukemia characteristics of patients in Felege Hiwot Referal Hospital.

VARIABLES	CATEGORIES	NO OF PATIENTS (%)	NO DEATH (%)
Sex	Female	175 (54.9)	29 (28.7)
	Male	137 (45.1)	72 (71.3)
Residence	Rural	218 (70.4)	80 (79.2)
	Urban	94 (29.6)	21 (20.8)
Marital	Unmarried	202 (15.0)	80 (79.2)
	Married	110 (34.8)	21 (20.8)
Education	Literate	239 (76.3)	56 (55.4)
	Illiterate	73 (23.7)	45 (44.6)
Anemia	No	239 (75.8)	61 (60.4)
	Yes	73 (24.2)	40 (39.6)
Stages of Chronic Lymphocytic Leukemia	Low	66 (20.7)	18 (17.8)
	Medium	67 (22.0)	20 (19.8)
	High	179 (57.3)	63 (62.4)

Table 2. Results of baseline characteristics of a continuous variable of Chronic Lymphocytic Leukemia patient's.

VARIABLES	N	MINIMUM	MAXIMUM	MEAN
Baseline age of patient's	312	16	85	56.73
Platelets	312	13	85	51.64
Hematocrit of patients	312	13	14	51.09
Hemoglobin of patients	312	15	85	47.86
Lymphocytes of patients	312	2	36.6	15.98
Red blood cell of patients	312	0	3	1.18

The results of the Cox proportional hazard model

The results of the Cox regression model, sex (male) of Chronic Lymphocytic Leukemia patients, age of Chronic Lymphocytic Leukemia patients, medium stage of Chronic Lymphocytic Leukemia patients, high stage of Chronic Lymphocytic Leukemia patients, and platelets of Chronic Lymphocytic Leukemia patients were positively associated /relation with time to death of Chronic Lymphocytic Leukemia of patients. Married marital status of Chronic Lymphocytic Leukemia patients, presence of anemia, hemoglobin, lymphocytic of Chronic Lymphocytic Leukemia patients, and red blood cells of Chronic Lymphocytic Leukemia patients were negatively associated with time to death of Chronic Lymphocytic Leukemia patients at a 5% level of significance. However, residence and educational status were insignificant at

Table 3. Final Cox proportional hazard model.

VARIABLES	ESTIMATE	STD.ERROR	HR	*P*-VALUE	CONFIDENCE INTERVAL	
					LOWER	UPPER
Age	2.43	0.34	11.36	<.001*	0.08	0.26
Sex (Ref = Female)						
Male	0.04	0.02	1.04	.004*	0.58	5.25
Marital (Ref = Unmarried)						
Married	−3.43	0.21	0.03	.003*	2.05	4.7
Stage (Ref = Low)						
Medium	0.26	0.88	1.29	.024*	−6.57	−2.68
High	0.69	0.31	1.99	<.001*	−4.86	−0.67
Anemia (Ref = No)						
Yes	2.35	0.30	10.49	.005*	0.31	0.63
Platelets	0.75	0.44	2.11	.007*	0.2	0.17
Hemoglobin	−3.87	0.59	0.02	<.001*	0.07	0.22
Lymphocytes	−1.23	0.75	0.29	.006*	0.03	0.29
RBC	−3.79	0.54	0.02	<.001*	0.09	0.25

*level *of significance of covariates at* 5%, Ref = reference of the categorical variable.

5% of the level of significance. The risk of Chronic Lymphocytic Leukemia patients increased by 11.36 (HR = 11.36, $P < .001$) for a unit increased in patients' age. The risk of deaths of the Chronic Lymphocytic Leukemia patients who were males was 1.04 (Hazard Ratio = 1.04, $P = .004$) times higher compared to the Chronic Lymphocytic Leukemia patients who were females. The risk of deaths of the Chronic Lymphocytic Leukemia patients who were the marital status of married was 0.03 (Hazard Ratio = 0.03, $P = .003$) times lower compared to the Chronic Lymphocytic Leukemia patients who were the marital status of unmarried. The risk of deaths of the Chronic Lymphocytic Leukemia patients who had at the medium stage was 1.29 (HR = 1.29, $P = .0241$) times higher compared to the Chronic Lymphocytic Leukemia patients who had at low stages. Similarly, the risk of deaths of the Chronic Lymphocytic Leukemia patients who had a high stage was 1.99 (HR = 1.99, $P < .001$) times higher compared to the Chronic Lymphocytic Leukemia patients who had a low stage. The risk of deaths of the Chronic Lymphocytic Leukemia patients who had anemia was 2.35 (Hazard Ratio = 0.09, $P < .005$) times the Chronic Lymphocytic Leukemia patients who had no Anemia. The risk of Chronic Lymphocytic Leukemia patients was increased by 2.11% (Hazard Ratio = 2.11, $P = .007$) for a unit increase in platelets. The risk of Chronic Lymphocytic Leukemia patients was decreased by 0.02(Hazard Ratio = 0.02, $P < .001$) for a unit increase in hemoglobin. The risk of Chronic Lymphocytic Leukemia patients was decreased by 0.29 (Hazard Ratio = 0.29, $P = .006$) for a unit increased in lymphocytes. The risk of Chronic Lymphocytic Leukemia patients was decreased by 0.02 (Hazard Ratio = 0.02, $P < .001$) for a unit increase in red blood cells (Table 3).

Discussion

The primary aim of this research was to determine the factors that influence the time to death of chronic lymphocytic leukemia patients at Felege Hiwot Referal Hospital in Bahir Dar, Ethiopia. In this research. Age is an important socio-demographic independent of time to death which means that the risk of Chronic Lymphocytic Leukemia increases with an increase in age. This result is consistent with another study,[13] The findings reveal that patients' age is a significant risk factor for Chronic Lymphocytic Leukemia. Gender had a substantial impact on the time it took for Chronic Lymphocytic Leukemia patients to die. Males were more likely than females to be diagnosed with Chronic Lymphocytic Leukemia. These findings are consistent with those of another study.[14] The marital status of Chronic Lymphocytic Leukemia patients had a substantial impact on the time to death. The findings suggest that a married person's marital status has a protective influence on Chronic Lymphocytic Leukemia disease survival outcomes, which is consistent with another study.[15] The type of Chronic Lymphocytic Leukemia stage had a substantial impact on the time it took for patients to die. Patients who were in the middle and late phases of the disease were at a higher risk. These findings are consistent with those of another study,[16] Individuals

who had been infected with anemic had a greater risk of death compared to patients who had not been infected with anemic. This finding is in line with the findings of another study,[17] a platelet is a clinically independent variable of time to death, and having too many or too few platelets, or platelets that don't function properly, might create difficulties. This research supports the findings of another study,[18] the result shows that the higher platelets were the main factor of Chronic Lymphocytic Leukemia patients. Hemoglobin is a clinical independent variable of time to death of having low hemoglobin level increasing the risk of Chronic Lymphocytic Leukemia patients. This result is in line with another study,[19] the result shows that lower hemoglobin was a significant factor in Chronic Lymphocytic Leukemia patients.

A lymphocyte is clinical independent of time to death, which means that the risk of Chronic Lymphocytic Leukemia increases with a decrease of lymphocytes. This result is consistent with another study,[6] the result shows that the lower lymphocytes were a significant risk factor for Chronic Lymphocytic Leukemia of patients. A red blood cell is a clinical independent variable of time to death of having low red blood cells increasing the risk of Chronic Lymphocytic Leukemia patients. This result is in line with another study,[20] Lower red blood cell counts or a lack of red blood cells were found to be a major factor in Chronic Lymphocytic Leukemia patients.

Conclusion

In summary, the independent variables age, sex, marital status, Chronic Lymphocytic Leukemia stage, presence of anemia, platelets, hemoglobin, lymphocytic, and red blood cells were substantially associated with time to death of Chronic Lymphocytic Leukemia patients, according to the study. Governments and concerned entities are paying more attention to reducing the risk of death in Chronic Lymphocytic Leukemia patients, with a focus on patients and the community as a whole.

Limitation

The study did not cover Chronic Lymphocytic Leukemia patients outside Bahir Dar Felege Hiwot referral Hospital. Lack of literature related to the subject under study. The study was based on secondary data, which may contain missing or skewed information, as well as certain key aspects not recorded on patients' files, such as socioeconomic status and nutritional state.

Acknowledgements

We acknowledged Felege Hiwot Referal Hospital, Bahir Dar, Ethiopia, for the availability of data for this research study, and we thank you Mr. Mitiku Wale, Mr. Setegn Muche, Mr. Solomn Sisay, Mr. dejen Gedamu, and Mis Bezanesh Melese to give us their comments, ideas, suggestion, and skills.

Authors' Contribution

Gedam Derbew Addisia has been in charge of the entire research process such as drafted the proposal, did the analysis, wrote the results, and prepared the manuscript. Awoke Seyoum Tegegne, and Denekew Bitew Belay participated in editing, analysis, prepared and critically revised the manuscript for its scientific content, and the remaining author's helps as technical issues. All authors read and approved the final manuscript.

Consent to participate and ethics approval

An ethical clearance certificate has been obtained from Bahir Dar University, Ethiopia. Hence, all of the authors have the appropriate permission for the data we used.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144:1941-1953.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
3. Reed JC. Chronic lymphocytic leukemia: a disease of dysregulated programmed cell death. *Clin Immunol Newsl*. 1997;17:125-130.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
5. Stauder R, Eichhorst B, Hamaker ME, et al. Management of chronic lymphocytic leukemia (CLL) in the elderly: a position paper from an international Society of Geriatric Oncology (SIOG) task force. *Ann Oncol*. 2017;28:218-227.
6. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. 2017;92:946-965.
7. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nat Rev Dis Primers*. 2017;3:1-22.
8. Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: an overview of the literature. *Eur J Cancer*. 2010;46:2647-2659.
9. Jain N, Gandhi V, Wierda W. Ibrutinib and venetoclax for first-line treatment of cll. Reply.. Replyundefined. *New Engl J Med*. 2019;381:789-2103.
10. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. *JAMA Oncol*. 2019;5:1749-1768.
11. Collett D. *Modelling Survival Data in Medical Research*. CRC press; 2015.
12. Rozman C, Montserrat E, Rodriguez-Fernandez JM, et al. Bone marrow histologic pattern—the best single prognostic parameter in chronic lymphocytic leukemia: a multivariate survival analysis of 329 cases. *Blood*. 1984;64:642-648.
13. Hosseini Teshnizi S, Taghi Ayatollahi SM. Comparison of cox regression and parametric models: application for assessment of survival of pediatric cases of acute leukemia in southern Iran. *Asian Pac J Cancer Prev*. 2017;18:981-985.
14. Milne K, Sturrock B, Chevassut T. Chronic lymphocytic leukaemia in 2020: the future has arrived. *Curr Oncol Rep*. 2020;22:36-39.
15. He X-K, Lin ZH, Qian Y, Xia D, Jin P, Sun LM. Marital status and survival in patients with primary liver cancer. *Oncotarget*. 2017;8:64954-64963.
16. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *New Engl J Med*. 2013;369:32-42.
17. Egbuna O, Zand MS, Arbini A, Menegus M, Taylor J. A cluster of parvovirus B19 infections in renal transplant recipients: a prospective case series and review of the literature. *Am J Transplant*. 2006;6:225-231.
18. Dmitrieva EA, Nikitin EA, Ignatova AA, et al. Platelet function and bleeding in chronic lymphocytic leukemia and mantle cell lymphoma patients on ibrutinib. *Journal of thrombosis and haemostasis : JTH*. 2020;18:2672-2684.
19. Jasuja GK, Ameli O, Reisman JI, et al. Health outcomes among long-term opioid users with testosterone prescription in the Veterans Health Administration. *JAMA Netw Open*. 2019;2:e1917141-e1917141.
20. Medearis DN, Minot GR. Studies on red blood cell diameter: II. In pernicious anemia, before, and during marked remission, and in myelogenous leukemia. *Trans Am Climatol Clin Assoc*. 1926;42:139-149.