Single Admission C-reactive protein Levels as a Sole Predictor of Patient Flow and Clinical Course in a General Internal Medicine Department

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ABSTRACT: **Background:** C-reactive protein (CRP) blood level is associated with clinical outcomes of several diseases. However, the independent predictive role of CRP in the heterogeneous population of patients admitted to internal medicine wards is not known.

Objectives: To determine whether single CRP levels at admission independently predicts clinical outcome and flow of patients in general medicine wards.

Methods: This study comprised 275 patients (50.5% female) with a mean age of 68.25 ± 17.0 years, hospitalized with acute disease in a general internal medicine ward. The association between admission CRP levels and clinical outcomes including mortality, the need for mechanical ventilation, duration of hospitalization, and re-admission within 6 months was determined.

Results: A significant association was found between CRP increments of 80 mg/L and risk for the major clinical outcomes measured. The mortality odds ratio (OR) was 1.89 (95% confidence interval [95%CI] 1.37–2.61, $P < 0.001$), mechanical ventilation OR 1.67 (95%CI 1.10–2.34, $P = 0.006$), re-admission within 6 months OR 2.29 (95%CI 1.66–3.15 $P < 0.001$), and prolonged hospitalization > 7 days OR 2.09 (95%CI 1.59–2.74, $P < 0.001$). Lower increments of 10 mg/L in CRP levels were associated with these outcomes although with lower ORs. Using a stepwise regression model for admission CRP levels resulted in area under the receiver operating characteristics curves between 0.70 and 0.76 for these outcomes.

Conclusions: A single admission CRP blood level is independently associated with major parameters of clinical outcomes in acute care patients hospitalized in internal medicine wards.

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KEY WORDS: C-reactive protein (CRP), internal medicine ward, mortality, re-admission, mechanical ventilation

Israeli public hospitals experience a chronic, ever-increasing shortage of hospital beds, reaching a low of 3.03 available beds per 1000 people in 2017 [1]. This shortage is more pronounced in the internal medicine wards and mostly in those wards admitting patients under acute care. This lack of available beds results in high rates of occupancy and a mean hospital stay of 3.9 days, which is among the lowest in the Organization for Economic Co-operation and Development (OECD) [2].

Internal medicine departments in public medical centers admit adult patients of all ages with a wide range of chronic and acute infectious, cardiovascular, and miscellaneous diseases. This extremely heterogeneous patient population leads to a very diverse hospital population. A number of different approaches have been suggested to predict the clinical outcomes of this heterogeneous population including calculating the overall patient disease burden, repeated determination of platelet counts, and a combination of several laboratory parameters such as albumin and inflammatory markers [3-6]. However, none of these complex approaches has gained widespread use in clinical practice. There is a need for a practical, simple, and standardized predictive tool enabling short-term planning of admission and discharge practices to optimize the usage of restricted facilities of these wards and manage patient flow.

C-reactive protein (CRP) is an acute-phase serum protein and a mediator of innate immunity [7,8]. CRP blood levels rise in various conditions of systemic inflammation. The use of CRP as a prognostic factor was assessed in a variety of diseases such as ischemic heart diseases, chronic obstructive pulmonary disease (COPD), and sepsis, with inconsistent results [9-14]. A strong correlation was observed between CRP levels, prognosis, and recurrent hospitalization in patients with ischemic heart disease and COPD [9]. However, the correlation of CRP to prognostic factors in patients with infectious diseases yielded conflicting results despite the wide and routine use in clinical practice [13-15].

Little is known regarding the independent prognostic significance of serum CRP levels in the mixed patient population admitted to the general wards of internal and geriatric medicine in public hospitals. To the best of our knowledge, only one previous study addressed this issue by showing that a very high

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initial serum CRP level (> 200 mg/L) as compared to lower levels was associated with poorer prognosis in patients admitted to an internal medicine department [8]. However, analysis of this association, according to cause of admission and/or stepwise increments in CRP levels, was not performed. It is also unknown whether higher initial CRP levels are associated with re-admission.

In this study we investigated whether a single CRP level determined at admission can be used as an independent prognostic tool of clinical course and other major clinical parameters affecting patient flow in a department of general internal medicine.

PATIENTS AND METHODS

The study was approved by the center's institutional ethics committee acting under the auspices of the Israeli Ministry of Health and according to the declaration of Helsinki.

This retrospective study comprised 275 patients hospitalized, due to acute disease, in the internal medicine ward at Assaf Harofeh Medical Center between 1 March 2013 and 30 June 2013. For all patients, blood CRP was measured at admission and their demographic, clinical, and laboratory data were collected [Table 1]. Data included age, gender, medical history, body mass index, fever at admission, white blood cell count, albumin, creatinine, and CRP level at admission. In addition, data regarding the duration of hospitalization (in days), the need for mechanical ventilation, mortality during the hospitalization, and recurrent hospitalization during the 6 months after the initial admission were collected. Fever at admission was defined as normal (up to 37°C), sub-febrile (37°C–38°C) or febrile (> 38°C) [13]. CRP blood level was tested using a Roche/Hitachi cobas 8,000 c701/702 system (Roche Diagnostics, Basel, Switzerland) (normal value < 5 mg/L). Patients that were admitted during the study period but were not tested for CRP at admission or were admitted for an elective procedure were excluded from the study.

Patients were divided into three diagnostic groups according to the main cause of their admission: infectious diseases including any type of infection; cardiovascular disorders including congestive heart failure, atrial fibrillation, or acute coronary syndrome; and miscellaneous diagnoses such as malignancies and their complications, hypertension, cerebrovascular attack, and thromboembolic events. The main cause of admission was indeterminable for four patients, so they were excluded from the subgroup analysis.

STATISTICAL ANALYSIS

Statistical analysis was conducted using BMDP software [16]. Analysis of variance (ANOVA) was used to compare continuous variables by groups, with Bonferroni's correction

Table 1. Patient characteristics

	All patients	Main reason for admission (n=271)			Difference among three subgroups (*P* value)
		Infectious disease	Cardiovascular disorders	Miscellaneous	
Number of patients	275 (100%)	96 (35%)	43 (16%)	132 (48)	
Age (years) mean ± SD	68 ± 17	66 ± 20	69 ± 16	70 ± 12	0.33
Males	136 (49.5%)	46 (47.9%)	24 (55.8%)	64 (48.5%)	0.66
Co-morbid conditions					
Congestive heart failure	54 (19.6%)	16 (16.7%)	15 (34.9%)	21 (15.9%)	‹ 0.05
COPD	59 (21.5%)	23 (24%)	10 (23.3%)	25 (18.9%)	0.63
Chronic renal failure	52 (18.9%)	16 (16.7%)	16 (37.2%)	20 (15.2%)	‹ 0.05
Ischemic heart disease	99 (36%)	28 (29.2%)	28 (31.1%)	41 (31.1%)	‹ 0.05
Smoking	257 (20.8%)	16 (16.7%)	15 (34.9%)	25 (18.9%)	‹ 0.05
Cerebrovascular disease	36 (13.1%)	19 (19.8%)	3 (7.0%)	14 (10.6%)	0.054
Drugs or alcohol abuse	7 (2.5%)	2 (2.1%)	3 (7.0%)	2 (1.5%)	0.14
Malignancy	36 (13.1%)	13 (13.5%)	4 (9.3%)	19 (14.4%)	0.69
Hypertension	155 (56.4%)	49 (51.0%)	26 (60.5%)	78 (59.1%)	0.41
Depression	87 (31.6%)	40 (41.7%)	11 (25.6%)	35 (26.5%)	0.034
Diabetes mellitus	101 (36.7%)	36 (37.5%)	24 (55.8%)	40 (30.3%)	‹ 0.05
Body mass index (kg/m^2) mean ± SD	28.4 ± 5.2	28.4 ± 5.3	27.5 ± 3.3	28.8 ± 5.6	0.55
Diastolic blood pressure (mmHg) mean ± SD	72 ± 17	69 ± 16	72 ± 13	75 ± 18	‹ 0.05
Systolic blood pressure mean ± SD	133 ± 27	124 ± 25	140 ± 23	136 ± 29	‹ 0.05
Laboratory data					
C-reactive protein on admission (mg/L) mean ± SD	61 ± 87	122.86 ± 105.25	23.66 ± 31.53	28.29 ± 54.78	‹ 0.001
Albumin (mg/dl) mean ± SD	36 ± 6	32 ± 6	38 ± 6	38 ± 6	‹ 0.001
White blood cell count (K/ml) mean ± SD	10.8 ± 6.8	13.3 ± 7.8	9.7 ± 4.5	9.3 ± 4.4	‹ 0.001
Thrombocytes (K/ml)	239 ± 104	252 ± 129	229 ± 83	235 ± 90	0.35
Creatinine mean ± SD	1.4 ± 1.43	1.3 ± 0.86	2.1 ± 2.5	1.3 ± 1.2	‹ 0.05
Fever					
Normal (‹ 37.0°C)	193 (70.2%)	28 (29.2%)	40 (93.0%)	122 (92.4%)	‹ 0.001
Sub-febrile (37.0°C–38.0°C)	42 (15.3%)	29 (30.2%)	3 (7.0%)	9 (6.8%)	‹ 0.001
Febrile (› 38.0°C)	38 (13.8%)	39 (40.6%)	0	1	‹ 0.001
Hospitalization in days, mean ± SD	6.8 ± 9	10.25 ± 13.31	5.84 ± 4.95	4.47 ± 4.14	‹ 0.001
Recurrent hospitalization (6 months following discharge)	123 (44.7%)	59 (61.5%)	24 (55.8%)	39 (29.5%)	‹ 0.001
Prolonged hospitalization (› 7 days)		32 (33.3%)	9 (20.9%)	14 (10.6%)	‹ 0.001
Mechanical ventilation	15 (5.5%)	9 (9.4%)	2 (4.7%)	4 (3.0%)	0.11
Deaths	17 (6.2%)	9 (9.4%)	1 (2.3%)	7 (5.3%)	0.23

COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein

for multiple tests. Pearson's Chi-square test or Fisher's exact test were used to compare discrete variables. Variables that did not have Gaussian distributions were transformed using either log-transformation (for CRP) or square root transformation (for length of hospitalization). We also examined correlations between various parameters using both Pearson's and Spearman's method. Logistic regression was used to determine the association between CRP at admission and various outcomes. A P value < 0.05 was considered statistically significant.

RESULTS

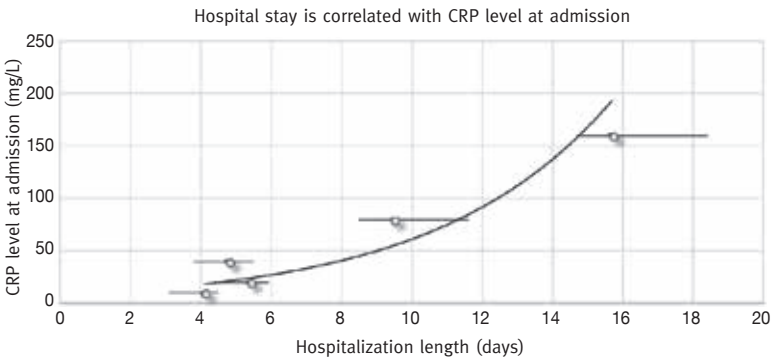
ASSOCIATION BETWEEN CRP AT ADMISSION AND DEMOGRAPHIC AND CLINICAL FACTORS

A stepwise logistic regression analysis was performed to determine whether the CRP level on admission was associated with any of the demographic, clinical, and major laboratory parameters. Duration of hospitalization was associated with high CRP levels (> 5 mg/dl) at admission in patients admitted with infectious diagnosis and no association was found in the cardiovascular group or miscellaneous group ($P < 0.001$).

Febrile patients were found to have higher CRP levels when compared to patients with normal body temperature at admission ($P < 0.001$). This correlation was stronger in patients with high fever (> 38°C) compared to patients with sub-febrile fever (36°C–37°C, $P < 0.05$). The only significant correlations with laboratory parameters on admission were a positive correlation for white blood cells count ($P < 0.001$) and a negative one for albumin levels ($P < 0.001$). No correlation was found between admission CRP and all other clinical, demographic, and laboratory parameters.

Figure 1. Duration of hospitalization in relation to CRP level at admission

Lenghth of hospital stay (days) is significantly correlated with higher CRP levels on admission (P ‹ 0.001). Length of stay rises sharply to approximately 10 days when CRP level on admission is › 80 mg/L and 15 days with CRP levels of 160 md/dl



CRP = C-reactive protein

ASSOCIATION BETWEEN ADMISSION CRP AND HOSPITALIZATION-RELATED AND PROGNOSTIC PARAMETERS

To determine whether admission CRP level predicts clinical disease course we evaluated the association of CRP levels with four major hospitalization-related clinical parameters. These were duration of hospital stay, the need for mechanical ventilation, mortality, and re-admission within 6 months.

As shown in Figure 1, mean hospital stay sharply increased from less than 5 days when admission CRP levels were less than 40 mg/dl, to approximately 10 days with CRP levels of 80 mg/dl, and 15 days with levels of 160 md/dl. This result shows a strong association between admission CRP and longer hospital stay ($P < 0.001$). Logistic regression using CRP levels demonstrated increased odds ratios (OR) for prolonged hospitalization with increasing increments of admission CRP levels [Table 2]. The OR for prolonged hospitalization of more than one week, reached 2.08 (95% confidence interval [95%CI] 1.59–2.74 $P < 0.001$) for every 80 mg/L increment. The need for mechanical ventilation also significantly increased with rising increments of CRP levels, reaching a maximal OR of 1.67 (95%CI 1.19–21.34 $P = 0.006$). A univariate analysis demonstrated that mortality was significantly higher among patients with high CRP at admission ($P < 0.001$). Further analysis by logistic regression revealed a stepwise association between increased admission CRP blood level and mortality, reaching a peak OR of 1.89 (95%CI 1.37–2.61 $P < 0.001$) for each 80 mg/L increment of CRP. A multivariate analysis demonstrated that the correlation between CRP and mortality was independent of gender and previous diagnosis of diabetes. The combined effect of increased age and CRP levels was higher than CRP alone reaching an OR of 2.06 for mortality (95%CI 1.28–3.31 $P < 0.001$). There was not enough data for analysis of a cor-

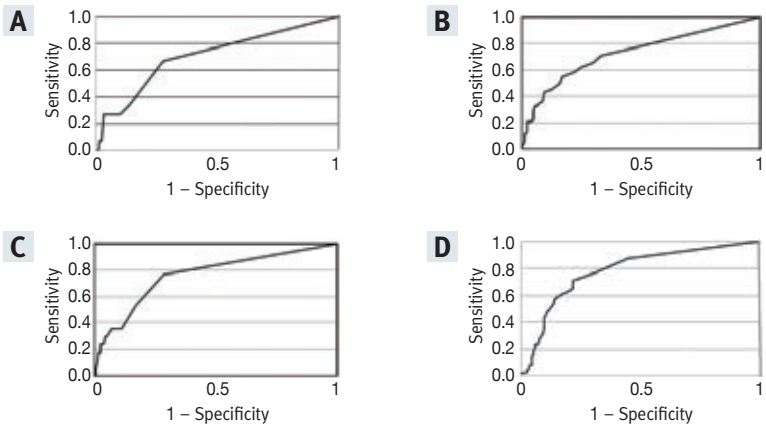
Table 2. Increased odds ratios for major clinical outcomes with gradual increments of admission C-reactive protein

	Increments of C-reactive protein on admission (mg/L)	Odds ratio	95% confidence interval	P value
Death	10	1.08	1.04–1.13	‹ 0.001
	40	1.38	1.17–1.62	‹ 0.001
	80	1.89	1.37–2.61	‹ 0.001
Prolonged hospitalization (› 7 days)	10	1.10	1.06–1.13	‹ 0.001
	40	1.44	1.26–1.66	‹ 0.001
	80	2.09	1.59–2.74	‹ 0.001
Recurrent hospitalization	10	1.11	1.07–1.15	‹ 0.001
	40	1.51	1.29–1.78	‹ 0.001
	80	2.29	1.66–3.15	‹ 0.001
Mechanical ventilation	10	1.07	1.02–1.11	0.006
	40	1.29	1.09–1.53	0.006
	80	1.67	1.19–2.34	0.006

relation between CRP and mortality in patients with other background diagnoses.

Logistic regression also showed that admission CRP was the strongest predictor of recurrent hospitalization with a gradual increase in CRP levels reaching an OR of 2.29 (95%CI 1.66–3.15 $P < 0.001$) for each 80 mg/L increment in CRP. Subgroup analysis according to three diagnosis groups revealed that mortality was associated with higher CRP levels only in patients with cardiovascular disease but not in the other two diagnostic groups while association between elevated CRP and the need for mechanical ventilation was found only in patients with infectious diseases (data not shown). An association between elevated CRP and recurrent hospitalization was the only significant finding in the miscellaneous diagnosis group. Receiver operating characteristics (ROC) curves for admission CRP and all four parameters revealed significant AUC ranging from 0.73 to 0.78 [Figure 2].

Figure 2. ROC curves for admission CRP and major clinical parameters
ROC curves for increasing CRP value upon admission level as a predictor of four clinical outcomes. The curves for all four outcomes revealed significant area under the curve ranging from 0.73 to 0.78 establishing the significant relationship between CRP levels and the outcomes. **[A]** Hospitalization longer than 7 days. **[B]** The need for mechanical ventilation. **[C]** Recurrent hospitalization within 90 days. **[D]** Mortality



CRP = C-reactive protein ROC = receiver operating characteristic

DISCUSSION

Internal medicine wards in Israeli general hospitals admit mainly acute care patients. The documented occupancy in these wards is extremely high, particularly during winter and seasonal influenza outbreaks, reaching 156% [2,17]. This admission rate includes a substantial percent of patients requiring mechanical or non-invasive ventilation. This overflow state and lack of space is associated with high morbidity and mortality, increased in-hospital acquired infection and elevated rates of re-admission [2]. As a result, these wards are forced to adopt an unacceptable rate of patient flow resulting in an average hospital stay of 3.9 days [2]. The number of available internal medicine beds in Israel is 0.5 beds per 1000 people, which is one of the lowest in the OECD and is likely to decrease further [2]. This severe imbalance between available beds and rate of admission is also likely to deteriorate in the near future. There is a crucial need for a simple and reliable prognostic algorithm allowing short-term prediction of major clinical outcomes in the heterogeneous patient population typical of internal medicine wards.

There is a need for a practical and applicable method to efficiently manage patient flow, allowing maximal utilization of available beds. Our logistic regression and ROC analysis clearly demonstrate that a single analysis of CRP blood level upon admission significantly associates with major clinical outcomes in acute care patients, particularly those outcomes that have an impact on occupancy. Thus, based on a single measurement of a non-specific laboratory parameter it might be possible to create a short-term predictive model of ward occupancy allowing better and more efficient use of ward resources in terms of hospital beds and medical manpower. Such a model should be validated by plotting large scale actual occupancy data of internal medicine wards as a function of admission CRP measurements in order to determine the range of CRP levels with the optimal predictive power.

Several general prognostic measures were previously offered as tools to predict hospitalization outcomes of patients with mixed diagnoses. The acute physiology, age, chronic health evaluation score as well as other general scores such as sepsis-related organ failure assessment, logistic organ dysfunction, and multiple organ dysfunction scores are routinely used in intensive care units to predict clinical outcomes of all patients, independently of their etiology at admission [18-21]. However, these relatively complex scores have been tailored to severely ill intensive care patients so are less applicable to the heterogeneous patient population of the internal wards.

Other approaches have also been suggested to predict the clinical outcomes of the heterogeneous patient population admitted to internal medicine wards including the patient's overall disease burden, repeated determination of platelet counts, and a combination of several laboratory parameters such as albumin and inflammatory markers such as IL-6 and erythrocyte sedimentation rate (ESR) [3,4,22]. For example, Lopes et al. [23] studied hypernatremia at admission as a prognostic factor and found an association with poor prognosis in hospitalized patients. Hospitalized patients with hypoalbuminemia had longer hospitalization, and tended to have higher ESR levels suggesting that blood albumin level could be used as a tool for patient evaluation [24]. Barchel and colleagues [3] found that hypoalbuminemia on admission to internal wards is correlated with poorer prognosis, and Robinson [25] found

that hypoalbuminemia during internal ward hospitalization was correlated with higher rates of re-admission within 30 days. These approaches focused on a limited number of clinical outcomes such as re-admission and/or mortality rather than a comprehensive analysis of several outcomes and their correlation with stepwise increments, and none of them gained wide use in clinical practice.

Similar to our results, an association between initial very high CRP levels > 200 mg/L and several prognostic parameters in patients admitted to an internal medicine department was demonstrated [8]. However, analysis of this association according to admission cause and/or stepwise increments in CRP levels was not performed, nor is it known whether higher initial CRP levels are associated with re-admission. A positive correlation was shown between the CRP level taken on the second day of hospitalization and length of stay of patients hospitalized for community acquired pneumonia (CAP) [15]. Although this study examined patients with a single hospitalization indication and not a heterogeneous patient population as we did, CAP is a common indication for hospitalization in the internal medicine ward and we find that their results affirm our current work.

Taken together, this data strongly suggests that any of these single laboratory parameters have limited practical value for the individual patient in general medicine wards and could be better used for the management of patient flow rather than predict the outcome of a single patient.

LIMITATIONS

The strongest correlations with clinical outcomes were found in patients admitted with acute infections and significantly elevated CRP levels as compared to patients with cardiovascular and miscellaneous diagnoses who had much lower admission CRP levels. This finding may suggest that the potential value of admission CRP as a clinical predictive marker in general internal medicine wards may be restricted only to those patients presenting with CRP levels above a certain threshold or to patients with acute infection. It could also indicate that the number of patients for any single admission cause should have been increased in order to draw more solid conclusions regarding admission CRP level and clinical outcome. Nevertheless, we believe that the clinical heterogeneity of our patients strengthens our findings as it reflects real life data and activity taking place in a representative general medicine ward. Moreover, as indicated throughout our paper, single admission CRP level could be utilized for predicting and managing patient flow of this heterogeneous patient population rather than focusing on one single clinical indication as has been done previously. Another limitation is that our study was limited to a single medical center and a limited number of patients. Thus, the interpretation of our results should be made with caution until further analysis of a larger data base and different types of internal medicine wards is completed.

CONCLUSIONS

Our findings demonstrate that a single measure of CRP level at admission to a general internal medicine ward independently predicts major clinical outcomes affecting ward occupancy and can be used for the management of patient flow in these wards.

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Capsule

Refining precision medicine

Unlike most colorectal cancer patients with mutations in the KRAS gene, those with the Gly13→Asp (G13D) mutation respond to blockade of epidermal growth factor receptor (EGFR). Using a systems biology approach, **McFall** and colleagues showed that EGFR-mediated activation of wild-type KRAS depended on whether the mutant KRAS inhibited the tumor suppressor neurofibromin 1 (NF1). Because the KRAS G13D mutant did not inhibit NF1, EGFR signaling still activated wild-type KRAS in KRAS G13D cells and drove tumor growth. These findings underscore how precision medicine could benefit from a systems-level analysis of patients.

Sci Signal 2019; 12: eaaw8288

Eitan Israeli

Capsule

Putting CAR T cells in idle

Chimeric antigen receptor T (CAR T) cells can be an effective cell therapy for cancer. Unfortunately, excessive activation of CAR T cells can occasionally cause severe, even lethal, toxicity. Existing approaches can suppress overactive CAR T cells, but these generally kill the CAR T cells, which abrogates both their toxicity and their antitumor effects. In contrast, **Mestermann** and co-authors dentified dasatinib as a drug that can temporarily inactivate CAR T cells. This helps reduce acute toxicity and allows the T cells to recover their anti-tumor effects after the drug is removed.

Sci Transl Med 2019; 11: eaau5907

Eitan Israeli

Capsule

Distinct immunology of the placenta

The placenta is formed when specialized cells from an embryo invade the maternal uterus. The effectiveness of this process can determine whether complications in pregnancy, such as preeclampsia, arise. In a perspective, **Colucci** discussed the emerging role of immune cells in the formation of the placenta. Homeostatic immune cell activities facilitate placental implantation without inducing an immune response to foreign antigens expressed on fetal-derived tissues. Understanding this process more fully could help to prevent or treat placenta-associated complications of pregnancy.

Science 2019; 365: 862

Eitan Israeli

"It has always seemed strange to me that in our endless discussions about education so little stress is laid on the pleasure of becoming an educated person, the enormous interest it adds to life. To be able to be caught up into the world of thought – that is to be educated"

Edith Hamilton (1867–1963), American educator and writer