

INFLUENZA SEASON 2019. ANALYSIS OF 143 HOSPITALIZED PATIENTS

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Abstract Influenza infection is a latent public health problem, affecting millions of people throughout the world, which imposes high morbidity and economic burden on the region. In Argentina, influenza-associated mortality is estimated at 6/100 000 person-years, and is higher among men \geq 65 years old. The knowledge of the baseline characteristics and outcomes of hospitalized patients is crucial for public health officials planning interventions to address local outbreaks. Thus, in this retrospective, single-center study, performed in a high-complexity university hospital, we aimed to analyze clinical characteristics, image findings, and laboratory variables of patients with laboratory-confirmed influenza requiring hospitalization in our hospital during 2019. Cases were confirmed by real-time reverse transcription-polymerase chain reaction. One hundred and forty-three patients with influenza were hospitalized during the study period; 141 (98.6%) were infected with influenza virus type A, including 88 (61.5%) with the H1N1 subtype. The median age was 71 years (IQR 60- 82), 111 (77.6%) were older than 70 years, and 126 (88.1%) had at least one coexisting illness; 56 (39.1%) patients required intensive care unit, 16 (11.1%) invasive mechanical ventilation, and 6 (4.1%) died during hospitalization. In this study, in-hospital mortality was similar to that reported in previous series of non-pandemic influenza, even though the majority of the cases in this study were older than 70 years and had at least one coexisting illness.

Key words: critical care, influenza, human, hospitalization, South America, Argentina, artificial respiration

Resumen *Temporada de influenza 2019. Análisis de 143 pacientes hospitalizados.* La influenza es un problema latente de salud pública que afecta a millones de personas en todo el planeta e impone una alta morbilidad y carga económica para la región. En Argentina, la mortalidad asociada a la influenza se estima en 6/100 000 personas-año y es mayor entre los hombres mayores de 65 años. El conocimiento de las características clínicas y la evolución de los pacientes hospitalizados es fundamental para planificar el abordaje de los brotes locales. En este estudio retrospectivo, realizado en un hospital universitario de alta complejidad, nuestro objetivo fue analizar las características clínicas, los hallazgos de imágenes y las variables de laboratorio en 143 pacientes con influenza confirmada por laboratorio que requirieron hospitalización durante 2019. Los casos fueron confirmados mediante la reacción en cadena de la polimerasa con transcripción inversa en tiempo real. El 98.6% (n: 141) estaban infectados por influenza tipo A y 61.5% (n: 88) correspondía al subtipo H1N1. La mediana de edad fue 71 años (IQR 60-82), el 77.6% (n: 111) tenía más de 70 años y el 88.1% (n: 126) al menos una enfermedad coexistente. El 39.1% (n: 56) requirió internación en unidad de cuidados intensivos, el 11.1% (n: 16) ventilación mecánica invasiva y seis pacientes (4.1%) fallecieron durante la hospitalización. En este estudio, la mortalidad hospitalaria fue similar a la publicada en series previas de influenza no pandémica, aunque la mayoría de los pacientes eran mayores de 70 años y presentaban al menos una enfermedad coexistente.

Palabras clave: cuidados críticos, influenza, humana, hospitalización, América del Sur, Argentina, respiración artificial

KEY POINTS

- Influenza infection is a global public health problem, affecting millions of people, with high morbidity and economic burden. In Argentina, influenza-associated mortality is estimated at 6/100 000 person-years, but it is higher among men \geq 65 years.
- Most patients in this study were older than 70 years and had at least one coexisting illness. However, in-hospital mortality was not higher than mortality reported in previous series of non-pandemic influenza. Bilateral lung compromise was more frequent among ICU patients compared with non-ICU patients in both chest x-rays and chest computed tomography. Hepatic enzyme impairment was more frequent in ICU patients. Additionally, proBNP was higher among ICU patients. A total of 39.1% of 143 hospitalized patients required admission to ICU.

Influenza is a latent public health problem, affecting millions of people throughout the planet. It is an important cause of morbidity and mortality, especially for certain susceptible populations^{1, 2}. Common risk factors for presenting a severe influenza disease are aging, cardiovascular disease, malignancy, immunosuppression, and end-stage organ failures like liver or chronic renal disease. Obesity and pregnancy have also been associated with an increased risk of negative outcome^{3, 4}.

Periodic changes in the antigenicity of the virus, and also bacterial co-infection, can lead to severe respiratory illness⁵. Approximately 30-40% of hospitalized patients with laboratory-confirmed influenza are diagnosed with acute pneumonia⁶ and admission to intensive care unit (ICU) ranges from 5 to 10%⁷. In Argentina, influenza-associated mortality is estimated at 6/100 000 person-years, and is higher among men \geq 65 years old⁸. Also, seasonal influenza imposes high morbidity and an increasing economic burden on the region⁹.

Knowledge of the baseline characteristics and outcomes of hospitalized patients is crucial for public health officials engaged in planning interventions to address local outbreaks. Thus, the objective of this study is to describe clinical characteristics, laboratory and imaging findings of patients who required hospitalization during 2019 in a high-complexity hospital located in Buenos Aires City.

Materials and methods

For this retrospective, single-center study, we recruited patients from January 1st to December 31st, 2019. Data were obtained from medical records of adult patients (18 years of age or older) with laboratory-confirmed influenza, hospitalized in a high-complexity university hospital located in Buenos Aires city.

All patients with influenza-like symptoms were screened at the emergency department. Influenza-like symptoms included sudden onset of fever, dyspnea, headache, cough, rhinorrhea,

muscle-ache, acute exacerbation of chronic obstructive pulmonary disease, gastrointestinal symptoms (such as nausea, vomiting, or diarrhea), and pneumonia. Hospital admission was decided by physicians based on patients' coexisting medical conditions, age, and acute onset of respiratory symptoms. Only those with confirmed influenza infection by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal-swabs were included. Other respiratory viruses including adenovirus, respiratory syncytial virus, parainfluenza viruses, rhinovirus, enterovirus, coronavirus, and bocavirus were also screened by RT-PCR.

On admission, patients were examined by chest x-rays (Rx) or chest computed-tomography scans (CTs), and laboratory testing. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, measures of electrolytes, procalcitonin, and pro-B-type natriuretic peptide (proBNP). Finally, the vaccination status was compiled from the medical record. Only patients who were vaccinated within the year were counted as immunized.

Clinical outcomes were followed up to March 2020. The study was approved by our hospital Ethics Committee in October 2019.

Categorical variables were summarized as counts and percentages and compared with the Fisher's exact test. Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Variables with normal distribution were tested by the t-test and variables without normal distribution were tested by the Mann-Whitney test. A two-tailed P-value $<$ 0.05 was considered significant. No imputation was made for missing data. We used STATA 13.0 for all analyses.

Results

Demographic and clinical characteristics of patients are shown in Table 1. Of the 143 patients included in the study, 79 were women and 64 were men. The median age was 71 years (IQR 60-82). Among the overall population, 111 (77.6%) were older than 70 years, and 113 (79%) had at least one coexisting illness. Chronic obstructive pulmonary disease was the most frequently observed (30.0%), followed by asthma, chronic heart disease, and active cancer, each one representing 11% (16 patients). Immunosuppression was registered in 26 patients (17.9%). In this subgroup, more patients with solid organ transplant remained at the general ward than in the ICU (12 [13.8%] vs. 1 [1.9%]; $p = 0.016$).

Fifty-six patients (39.1%) required ICU admission and the rest were treated in the general ward. Sixteen patients (11.1%) underwent invasive mechanical ventilation and 40 (27.9%) non-invasive ventilation or high-flow nasal cannula. Five (9%) of the 56 patients requiring ICU died. The average length of stay was 7 days (IQR 4-13) for all patients, 5 days (IQR 3-10) for those who did not require ICU, and 10 days (IQR 6-16) for those who did.

The vaccination status was known in all cases, with a vaccination rate of 32.1% (28) in non-ICU patients and 26.7% (15) in ICU patients. Three (6.9%) vaccinated and 13 (13%) unvaccinated patients required invasive mechanical ventilation ($p = 0.39$).

TABLE 1.– Influenza season 2019: characteristics of 143 hospitalized patients

	All patients (n = 143)	ICU (n = 56)	non-ICU (n = 87)
Male sex, % (no.)	44.7 (64)	41.1 (23)	47.2 (41)
Age, years			
Median (IQR)	71 (60 - 82)	74 (72 - 84)	69 (58 - 80)
Distribution, % (no.)			
≤ 39 years	8.4 (12)	3.5 (2)	11.5 (10)
40-59 years	14.0 (20)	14.2 (8)	13.8 (12)
60-79 years	45.5 (65)	44.6 (25)	46.0 (40)
≥ 80 years	32.2 (46)	37.5 (21)	28.7 (25)
Signs and symptoms, % (no.)			
Fever	65.0 (93)	53.5 (30)	72.4 (63)
Dyspnea	58.0 (83)	69.6 (39)	50.5 (44)
Cough	52.4 (75)	51.7 (29)	52.8 (46)
Rhinorrhea	19.5 (28)	14.2 (8)	22.9 (20)
Confusion	7.6 (11)	8.9 (5)	6.8 (6)
Muscle ache	6.9 (10)	7.1 (4)	6.8 (6)
Gastrointestinal symptoms	4.8 (7)	1.7 (1)	6.8 (6)
Chronic illness, % (no.)	79 (113)	77.3 (41)	82.7 (72)
COPD	30 (43)	23.2 (13)	34.4 (30)
Asthma	11 (16)	12.5 (7)	10.3 (9)
Chronic heart disease	11 (16)	16.7 (9)	8 (7)
Active cancer	11 (16)	7.4 (4)	13.8 (12)
Coronary disease	8.3 (12)	13 (7)	5.7 (5)
Cognitive impairment	7.6 (11)	11.1 (6)	5.7 (5)
Diabetes	5.5 (8)	3.7 (2)	6.9 (6)
Obesity	6.2 (9)	7.4 (4)	5.7 (5)
Chronic renal disease	3.4 (5)	7.4 (4)	1.1 (1)
Active smoking	1.4 (2)	0	2.3 (2)
Immunosuppression, % (no.)	17.9 (26)	11.1 (6)	23 (20)
Solid organ transplant	9 (13)	1.9 (1)	13.8 (12)
Corticosteroid use*	9 (13)	9.3 (5)	9.2 (8)
Vaccination status, % (no.)			
Vaccinated	30.0 (43)	26.7 (15)	32.1 (28)
Ventilatory support, % (no.)			
Invasive	11.1 (16)	28.5 (16)	-
Non-invasive	27.9 (40)	53.5 (30)	11.4 (10)
NIV	16.8 (24)	30.3 (17)	8.0 (7)
HFNC	11.1 (16)	23.2 (13)	3.4 (3)
Clinical outcome, % (no.)			
Discharged	95.8 (137)	91.0 (51)	98.8 (86)
Dead	4.2 (6)	9.0 (5)	1.2 (1)

ICU: intensive care unit; IQR: interquartile range; COPD: Chronic obstructive pulmonary disease; NIV: non-invasive ventilation; HFNC: high-flow nasal cannula

*Meprednisone > 4 mg/day, or equivalent

A total of 141 (98.6%) patients were infected by influenza virus type-A, 88 (61.5%) by subtype H1N1, and 53 (37.0%) by H3N2. Most cases were reported during the 24th to 32nd epidemiological weeks (winter season) of the Southern hemisphere. The temporal distribution and the distribution of cases by viral type and subtype are detailed in Figures 1 and 2.

Coinfection with other respiratory viruses was detected in 22 (15.3%) patients. Rhinovirus (n: 7 [74.8%]) was the most frequently registered, followed by respiratory syncytial virus (n: 6 [4.1%]), coronavirus (n: 3 [2.0%]), parainfluenza (n: 3 [2.0%]), adenovirus (n: 2 [1.3%]), and bocavirus (n: 1 [0.6%]).

Fig.1.- Influenza season 2019. Annual distribution of 143 cases

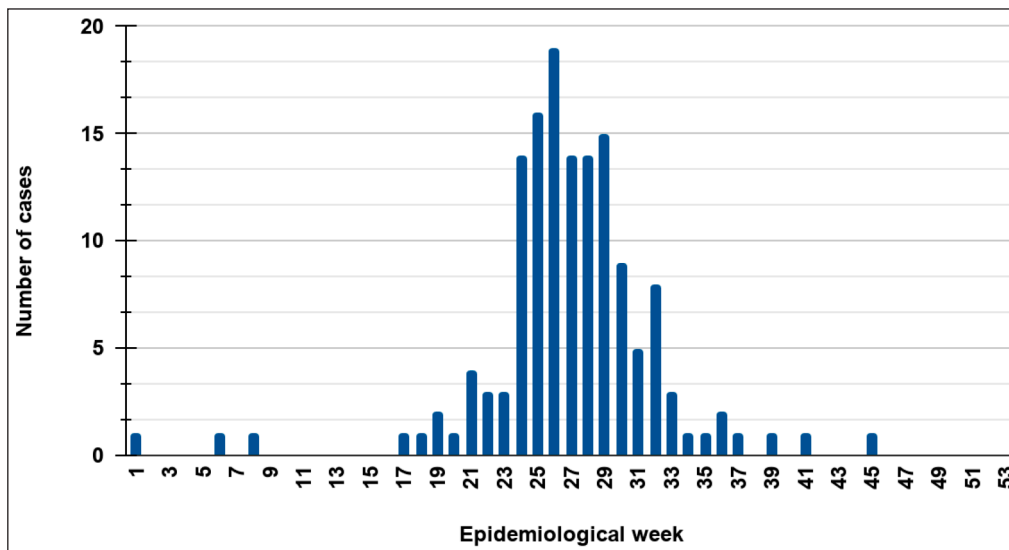
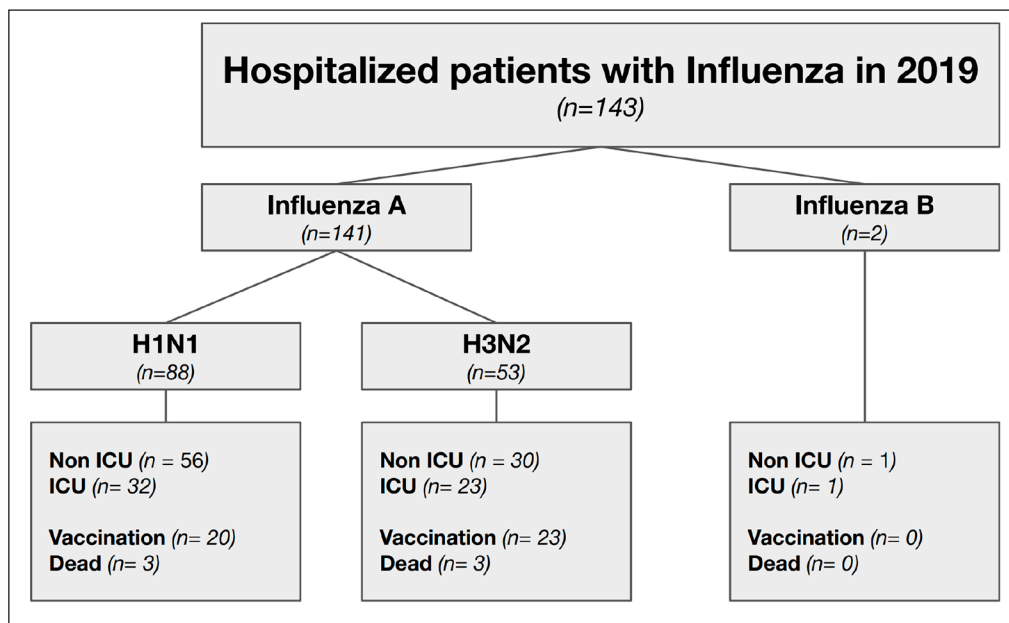


Fig.2.- Distribution of cases by viral type and subtype



ICU: intensive care unit

Regarding clinical findings on admission, fever was present in 93 (65.0%) patients. The second most common symptom was dyspnea in 83 (58.0%), followed by cough (n: 75 [52.4%]) and rhinorrhea (n: 28 [19.5%]); diarrhea, nausea, or vomiting (n: 7 [4.8%]) were uncommon. Dyspnea was more frequent in ICU patients (n: 39 [69.6%] vs. n: 44 [50.5%]; p = 0.0257).

Table 2 shows laboratory findings. ICU patients presented significantly higher proBNP levels than non-ICU patients (28 [50.0%] vs. 11 [12.6%]; p < 0.001). Hepatic enzyme impairment was more frequent in ICU patients than in non-ICU patients (aspartate aminotransferase, n: 21 [37.5%] vs. n: 7 [8.0%]; p<0.001 and alanine aminotransferase, n: 14 [25%] vs. n: 5 [5.7%]; p = 0.0018). No associated involvement of alkaline phosphatase, bilirubin, or prothrombin time was observed.

Table 3 shows Rx and CT imaging findings. Of 129 Rx performed at admission, 83 (67.4%) revealed abnormal results. The most common patterns observed were: interstitial opacity (35.6%), consolidation (24.8%), and pleural effusion (6.9%). Also, 33.3% of the patients presented bilateral compromise. Moreover, almost all ICU cases (50

[98.1%]) showed pathological findings in Rx in contrast with admissions to general ward (37 [47.4%]). A total of 85 chest CTs were performed. No CT abnormality was found in 11 (12.9%) studies. Ground-glass opacity was found in 34.1%, followed by consolidation in 29.4%, tree in bud sign in 15.2%, and multiple mottling opacity in 8.2%. Bilateral compromise was informed in 44.7% and pleural effusion in 14.1%. Bilateral compromise was more frequent among ICU patients compared with non-ICU patients in both chest Rx (26 [50.9%] vs. 17 [21.7%]; p<0.001), and chest CT (23 [67.6%] vs. 15 [29.4%]; p = 0.002).

Discussion

In this cohort study, we report clinical characteristics and risk factors associated with clinical outcomes in patients with laboratory-confirmed influenza who required hospitalization during 2019. We found that the overall mortality was similar to that reported in previous series. Noticeably, ICU-mortality was lower despite the fact that the majority of the cases reported in our study were older than 70 years

TABLE 2.- Laboratory findings

	All patients (n = 143)	ICU (n = 56)	non-ICU (n = 87)
Blood test findings, median (IQR)			
Leucocytes per mm ³	8140 (5113 - 11 725)	9199 (6350 - 12 452)	7680 (4528 - 10 709)
Neutrophils per mm ³	6337 (3720 - 9310)	7274 (4086 - 10 979)	5702 (3461 - 8029)
Lymphocytes per mm ³	749 (454 - 1234)	746 (377 - 1149)	794 (497 - 1264)
Platelets per mm ³	198 700		
(150 075 - 254 700)	207 650		
(164 375 - 260 600)	187 000		
(1492 50 - 245 575)			
Prothrombin time, s	79 (68 - 94)	76 (64 - 93)	81 (70 - 94)
Urea, mg/dl	41 (33 - 53)	41 (33 - 56)	41 (30 - 52)
Creatinine, mg/dl	0.97 (0.76 - 1.26)	0.98 (0.77 - 1.23)	0.96 (0.77 - 1.28)
Sodium, mmol/l	135 (132 - 137)	135 (132 - 138)	135 (132 - 137)
Potassium, mmol/l	4.1 (3.7 - 4.5)	4.1 (3.8 - 4.5)	4.0 (3.6 - 4.5)
Total bilirubin, mg/dl	0.5 (0.4 - 0.8)	0.6 (0.4 - 0.8)	0.5 (0.4 - 0.8)
Alkaline phosphatase, UI/l	72 (59 - 85)	71 (59 - 89)	73 (59 - 84)
Aspartate aminotransferase ,UI/l	23 (18 - 34)	29 (20 - 47)	21 (16 - 28)
Alanine aminotransferase, UI/l	19 (13 - 29)	21 (15 - 34)	17 (12 - 22)
Albumin, g/dl	3.7 (3.3 - 4.0)	3.6 (3.2 - 4.1)	3.7 (3.4 - 4.1)
Procalcitonin, ng/ml	0.17 (0.07 - 0.97)	0.14 (0.08 - 0.41)	0.08 (0.06 - 0.50)
proBNP, pg/ml	2000 (659 - 4125)	2750 (1083 - 8911)	1361 (537 - 2341)

ICU: intensive care unit; IQR: interquartile range; proBNP: pro b-type natriuretic peptide

TABLE 3.- *Imaging findings*

Chest x-ray findings, % (no.)	All patients n = 129	ICU n = 51	non-ICU n = 78
Normal	32.6 (42)	2.0 (1)	52.6 (41)
Pathological	67.4 (87)	98.0 (50)	47.4 (37)
Interstitial opacity	35.7 (46)	50.9 (26)	25.6 (20)
Consolidation	24.8 (32)	35.2 (18)	17.9 (14)
Pleural effusion	7.0 (9)	11.6 (6)	3.8 (3)
Bilateral compromise	33.3 (43)	50.9 (26)	21.7 (17)
Chest CT findings, % (no.)	n = 85	n = 34	n = 51
Normal	12.9 (11)	2.9 (1)	19.6 (10)
Pathological	87.1 (74)	97.1 (33)	80.4 (41)
Ground-glass opacity	34.1 (29)	41.2 (14)	29.4 (15)
Consolidation	29.4 (25)	38.2 (13)	23.5 (12)
Tree-in-bud sign	15.3 (13)	11.8 (4)	17.6 (9)
Multiple mottling opacity	8.2 (7)	5.9 (2)	9.8 (5)
Bilateral compromise	44.7 (38)	67.6 (23)	29.4 (15)
Pleural effusion	14.1 (12)	26.5 (9)	5.9 (3)

ICU: intensive care unit; CT: computed-tomography

and had at least one coexisting illness¹⁰⁻¹⁴. Also, the relative number of patients admitted to ICU was higher. This may be attributed to the fact that age is not a restriction for invasive vital support in our ICU.

As regards chronic medical illnesses, we found a lower number of solid organ transplant patients hospitalized in ICU than in the general ward. Immunocompromised individuals, such as organ transplant recipients, are generally deemed to be at an increased risk of morbidity and mortality from influenza infection^{15, 16}. Nevertheless, our results are similar to those of a recent report showing that immunosuppressed patients had better outcomes and less organic failures than those who were immunocompetent. Stahl et al. found differences in ICU admission in immunocompetent vs. immunosuppressed patients (14% vs. 7%, $p = 0.07$), as well as in the requirement of mechanical ventilation (11% vs. 4%, $p = 0.41$), vasopressors (12% vs. 3%, $p = 0.01$), and mortality (12% vs. 3%, $p = 0.23$)¹⁷. In this sense, severe influenza infection is often associated with a hyperinflammatory phenotype, most likely the consequence of a dysregulated host response to influenza similar to sepsis, explaining the better outcomes observed among immunosuppressed patients^{18, 19}. It would be interesting to deepen the analysis of clinical and immunological characteristics of influenza in this group of patients to draw conclusions and extrapolate information to the general population.

In relation to the laboratory findings, the impairment of hepatic enzymes, mainly aspartate aminotransferase (ASAT), was far more frequent in ICU patients. In a recently published research, an ASAT value superior to 88 IU/l was identified as a better predictor of 3-month mortality (hazard ratio 7.68 [IC 95% 1.6-35.1]) than other variables such as creatinine and PaO₂/FiO₂²⁰. Additionally, proBNP was higher in ICU patients. High levels of ProBNP have been reported to predict poor prognosis in patients with confirmed influenza²¹.

Regarding imaging studies, in our series only one patient of those requiring ICU had a normal result. More extensive lung compromise was seen in ICU cases, with more frequent bilateral involvement in both chest Rx and chest CTs in comparison with non-ICU patients. Similar data were found in other series where a higher percentage of pathological radiographic findings were detected in patients with a worse prognosis²²⁻²⁴.

Our study has several limitations. It is an observational study of a single center and data from other Argentine centers are necessary to know the impact of influenza in hospitalizations. Also, as previously noted, no post-ICU follow up was performed.

We conclude that in 2019 both the mortality and the severity of the cases were similar to those published in previous series of non-pandemic influenza. Analysis of annual data would be valuable to document the severity of

influenza hospitalizations by age-group and comorbidities according to the circulating influenza viruses. Multicenter data are needed to get a more complete picture of the hospitalization burden related to influenza.

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Conflict of interest: None to declare

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Parece que los chinos dicen que un dibujo vale más que mil palabras. Lo que nadie sabe es cuánto vale una sola palabra. Pero todo el mundo sabe cuánto vale un dibujo. Es una moneda universal y no está corrompida. No necesita del habla, de la lengua, de los estados de lengua, del lenguaje. Es natural, como el agua, como la sed. Sin embargo, no hay un dibujo igual a otro dibujo, una línea igual a otra línea, un ser humano igual a otro ser humano.

Isidoro Blaisten (1933-2004)

Anticonferencias. Buenos Aires: Emecé, 1983. Sobre los dibujos de Fati; p189-90